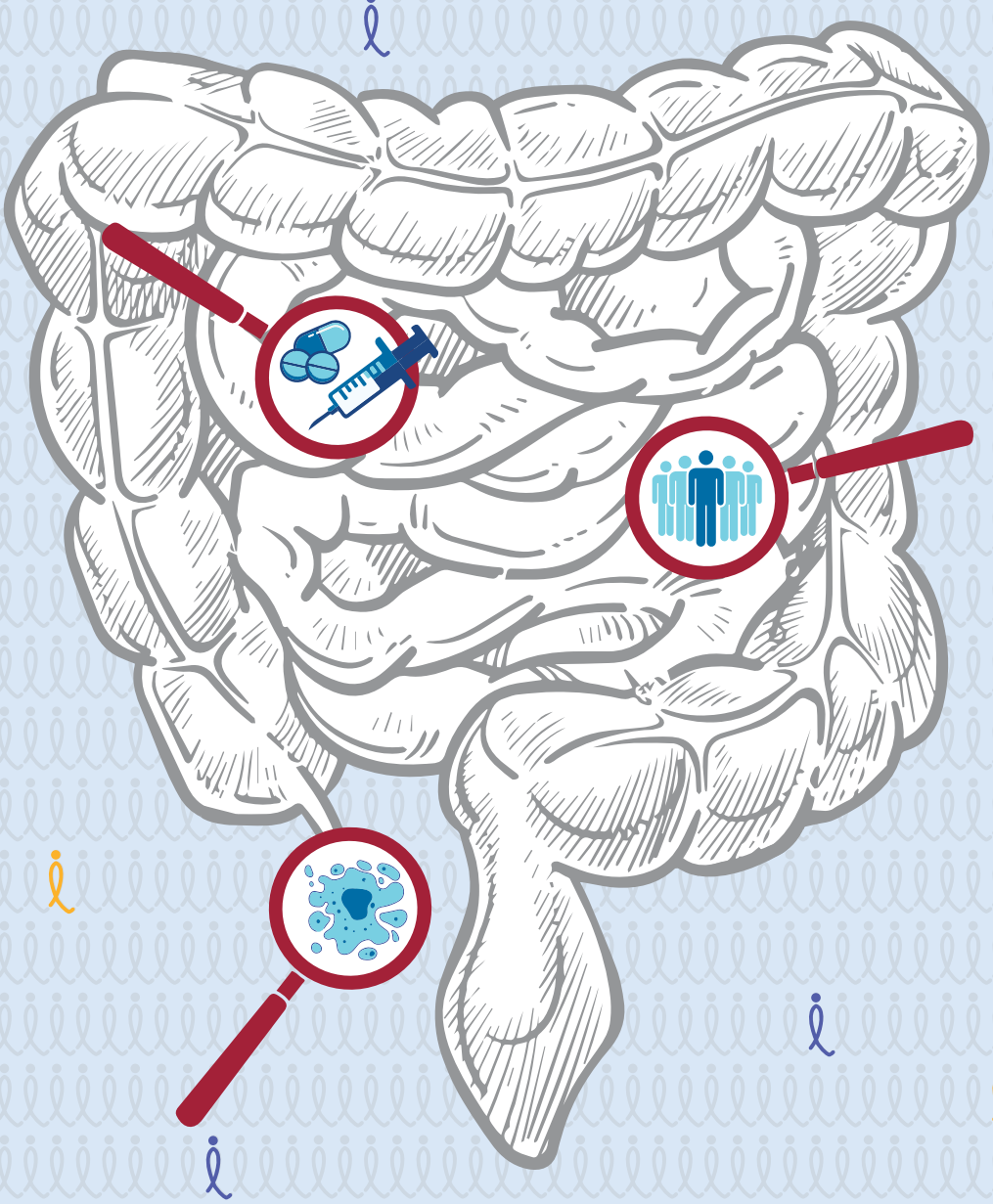
Clinical and Pathological Aspects of Small Bowel and Appendiceal Cancer

Insights into rare entities



Laura M. Legué

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Insights into rare entities

Laura Maria Legué

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Clinical and Pathological Aspects of Small Bowel and Appendiceal Cancer

Insights into rare entities

Klinische en pathologische aspecten van dunne darm- en appendixkanker

Inzichten in zeldzame ziekte-entiteiten

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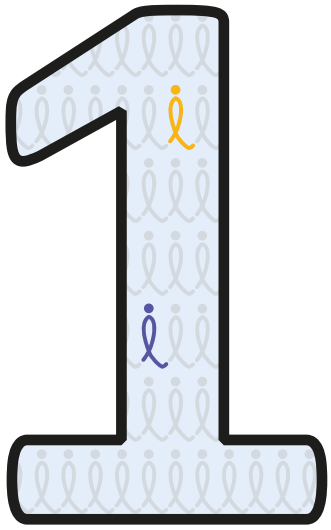
Table of contents

Chapter 1	General introduction	7
Part I	**Epidemiology of small bowel cancer**	19
Chapter 2	Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: A population-based study in the Netherlands	21
Chapter 3	Synchronous peritoneal metastases of small bowel adenocarcinoma: Insights into an underexposed clinical phenomenon	39
Part II	**Palliative systemic therapy in metastatic small bowel cancer**	57
Chapter 4	Palliative chemotherapy for patients with synchronous metastases of small bowel adenocarcinoma: A reflection of daily practice	59
Chapter 5	Addition of bevacizumab to first-line palliative chemotherapy in patients with metastatic small bowel adenocarcinoma: A population-based study	75
Part III	**Histologic subtype in appendiceal cancer**	91
Chapter 6	Review: Pathology and its clinical relevance of mucinous appendiceal neoplasms and pseudomyxoma peritonei	93
Chapter 7	The prognostic relevance of histologic subtype in appendiceal adenocarcinoma	111
Chapter 8	The clinical relevance of the histopathological classification for metastatic mucinous appendiceal neoplasms in a verified population-based cohort	127
Chapter 9	Summary and general discussion	143
Nederlandse samenvatting (Dutch summary)		165
List of publications		173
Dankwoord (acknowledgements)		177
Curriculum vitae		183
PhD portfolio		187

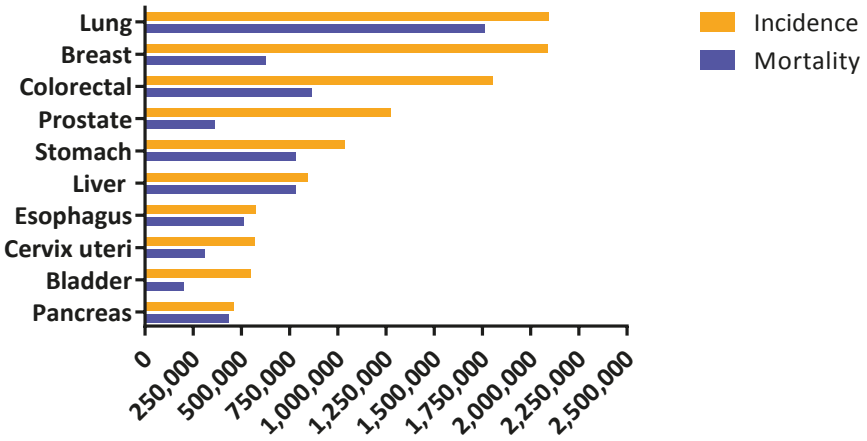


General introduction

General introduction

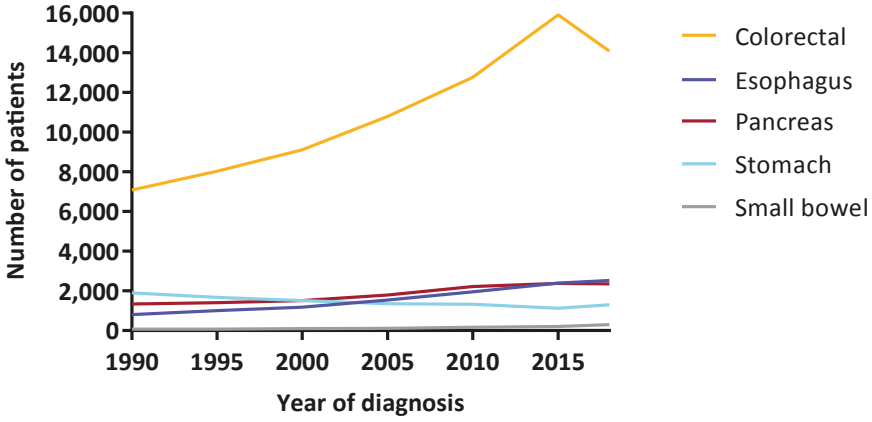
Gastrointestinal cancer represents a significant disease burden, and is one of the leading causes of cancer-related mortality worldwide (figure 1)[1, 2]. The gastrointestinal tract comprises of all organs responsible for digestion, including the accessory organs liver, gallbladder, biliary tract and pancreas. The most common gastrointestinal malignancy is colorectal cancer, which ranks globally third in incidence rate, and even second in mortality rate, as it solely accounts for approximately 1 in 10 cancer-related deaths[1]. Other highly incident gastrointestinal cancers include liver, gastric and esophageal cancer, all listed in the top 10 of incidence and mortality rates worldwide[1]. However, malignancies of several other gastrointestinal sites are scarce with crude incidence rates less than 6 per 100.000, including the gallbladder and extrahepatic bile duct, small bowel, appendix and anal canal[3]. An overview of the distribution of the incidence of several gastrointestinal cancers in the Netherlands is shown in figure 2[4].

Figure 1. Incidence and mortality of the most frequent solid cancers worldwide in 2018.



Source: Bray et al, GLOBOCAN[1]

Figure 2. Incidence of several gastrointestinal cancers in the Netherlands by year of diagnosis.



Source: Netherlands Cancer Registry

Most recent research has focused on the most frequently encountered gastrointestinal malignancies. As small bowel and appendiceal cancers are rare, these malignancies have not been well studied. In daily clinical practice, patients with small bowel or appendiceal cancer are consequently mostly treated in a similar fashion as frequently studied gastrointestinal cancers, as colorectal cancer or gastric cancer[5]. However, it is largely unknown if the treatment options for colorectal and gastric cancer can be extrapolated for the treatment of small bowel and appendiceal cancer.

Small bowel cancer

Despite the length of the small bowel within the gastrointestinal tract, small bowel cancer is only encountered in 2-3% of all gastrointestinal cancers. Multiple theories are suggested to clarify the rarity of small bowel cancer, including the rapid transit time of the nutritional elements in the small bowel, more alkaline environment, lower bacterial load and the rapid turnover of the mucosal area[6, 7]. Small bowel adenocarcinoma (SBA) is the most common histologic subtype, accounting for almost 40% of the tumours[8]. Etiology is largely unexplained, although an adenoma-carcinoma driven sequence analogous to the development of colorectal cancer has been suggested. However, molecular alterations in SBA and colorectal cancer differ greatly, with especially distinct differences in the mutational status of the adenomatous polyposis coli (APC) gene[6, 9, 10].

Multiple risk factors for SBA are identified, including celiac disease, Crohn's disease and hereditary syndromes, such as hereditary non-polyposis colon cancer (HNPCC; Lynch

syndrome), familial adenomatosis polyposis (FAP) and Peutz-Jeghers syndrome[7-9]. Celiac disease and Crohn's disease both cause an immunological response with chronic inflammation in either the proximal or distal small bowel, respectively, which results in an 80-fold increased relative risk for dysplasia and SBA compared to the general population[7, 9, 11, 12]. Other lifestyle associated risk factors include the high consumption of sugar, refined carbohydrate, alcohol, smoking and red meat[9, 13].

Symptomatology in patients with SBA is generally nonspecific, like abdominal pain, weight loss, gastrointestinal bleeding or anemia or an acute clinical presentation with bowel obstruction[8, 9]. Diagnosis can also be challenging, as the small bowel beyond the distal duodenum or above the terminal ileum is difficult to access for endoscopic examination with either gastroscopy or colonoscopy, causing an average delay until diagnosis of approximately 6-8 months[8]. Moreover, it has been hypothesized that due to the combination of nonspecific symptoms and the lack of simple diagnostic tools, metastatic disease is common, with approximately 40% of the patients presenting with metastatic SBA[8, 9, 14]. Though, guidelines on the effectiveness of systemic therapy and the preferred treatment options for patients with metastatic disease are absent.

Appendiceal cancer

The incidence of appendiceal cancer is also very rare, accounting for less than 0.5% of all gastrointestinal cancers and occurring in less than 2% of all appendectomies[15, 16]. Appendiceal cancer is often rarely considered or diagnosed preoperatively, as typical and specific symptoms are lacking. General symptoms include vague acute or chronic abdominal pain or symptoms resembling acute appendicitis[15, 17, 18]. Also the incidence of diagnosing appendiceal cancer coincidentally during surgical intervention for another indication is high[15].

The most frequently encountered malignant subtype is the adenocarcinoma, accounting for 50-70% of the cases[17, 19-21]. Appendiceal adenocarcinomas are subdivided into the mucinous, non-mucinous and signet ring cell histologic subtype[16, 22]. Histologic subtype is thought to be of clinical relevance, as historic research showed that patients with a mucinous appendiceal adenocarcinoma have a better or comparable clinical outcome, compared to non-mucinous adenocarcinomas[16, 17, 20, 22].

Mucinous and signet ring cell adenocarcinomas belong to the subgroup of mucinous appendiceal neoplasms, which have been of great interest, as these tumours are the leading cause of pseudomyxoma peritonei[22, 23]. Pseudomyxoma peritonei is a rare peritoneal disease, characterized by progressive accumulation of mucinous ascites and mucinous

tumour deposition[23-26]. In recent years, new insights were gathered with regard to mucinous appendiceal neoplasms and its relation to pseudomyxoma peritonei[23, 27-34]. In 2017, an international expert panel on behalf of the Peritoneal Surface Oncology Group International published an innovative and overarching consensus-based histopathological classification for mucinous appendiceal neoplasms and pseudomyxoma peritonei[27]. With this classification, clear and universal definitions for mucinous appendiceal neoplasms were specified, which could be distinguished into true premalignant lesions or adenomas, tumours of uncertain malignant potential, known as low-grade mucinous appendiceal neoplasms and high-grade mucinous appendiceal neoplasms, and malignant lesions, including mucinous and signet ring cell adenocarcinomas[27].

As previous research regarding appendiceal cancer did not use this histopathological classification, it is possible that tumours of uncertain malignant potential with a more favourable prognosis in both locoregional and metastatic disease, were falsely classified as mucinous appendiceal adenocarcinomas and consequently, incorrectly influenced the results of treatment.

Rarity of small bowel and appendiceal cancer and the lack of trials

Due to the rarity of small bowel and appendiceal tumours, prospective cohort studies or randomized controlled trials are nearly impossible to conduct. Most research regarding small bowel and appendiceal tumours derive from small phase II-studies or retrospective databases of specialised or referral centres, which causes inevitable selection bias. Moreover, due to the lack of studies, no guideline exist how to treat these patients. However, clinicians are still confronted with these patients in daily practice, which challenges them to decide which treatment suits best.

The need for population-based studies

In the area of rare diseases as in small bowel and appendiceal cancer, population-based research is highly valuable in providing important clinical insights into basic epidemiology, prognostic factors and the use and effects of treatment, as more patients over time could be enrolled, compared to other observational studies or randomized controlled trials[35]. Due to the higher number of patients with a rare cancer in an unselected population, the obtained results are both a reflection of the clinical disease course and the delivered care to these patients in daily practice. Consequently, these results could be useful for a potential guideline for treating physicians in daily clinical practice.

Data sources

The data sources for the studies included in this thesis were the Netherlands Cancer Registry

and the Dutch Pathology Registry.

Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) is a nationwide population-based registry, which collects data on all newly diagnosed malignancies in the Netherlands since 1989. It is managed by the Netherlands Comprehensive Cancer Organisation (IKNL), consisting of 9 regions throughout the Netherlands, which covers the entire Dutch population of nearly 17 million inhabitants. Primary source of notification is the Dutch nationwide network and registry of histo- and cytopathology (PALGA), accompanied with data from the National Registry of Hospital Discharge Diagnoses and radiotherapy institutions. Information on patient and tumour characteristics, diagnosis and initial treatment is routinely collected by registry clerks from the medical records. In the NCR, all primary tumours are staged and registered according to the Tumour Node Metastasis (TNM) classification[36]. The topographical site of the primary tumour and systemic metastases are registered according to the third version of the International Classification of Disease for Oncology (ICD-O)[37]. Information of the vital status of patients is annually obtained through linkage of the NCR with civil municipal registries and the central bureau for genealogy, in which data of all deceased and emigrated inhabitants of the Netherlands are collected.

Additional data collection

In the NCR, extensive data on the type and duration of systemic therapy of small bowel cancer is not routinely collected. Fortunately, with financial support of the Catharina Research Fund, additional data on systemic treatment regimens for patients treated with palliative systemic therapy for synchronous metastases of SBA diagnosed between 2007 and 2016 was retrospectively collected by registry clerks of the NCR in March of 2018. The additional data comprised information on first-, second- and third-line systemic treatment regimens, including details and duration of the chemotherapeutical and targeted agents.

Dutch Pathology Registry (PALGA)

In appendiceal cancer, multiple tumour classifications for appendiceal mucinous neoplasms and various interpretations of the invasive aspect of these lesions existed over time. As cancer registries only collect data on invasive malignancies, data on previously assumed non-malignant lesions as tumours of uncertain malignant potential, are not routinely registered in locoregional disease. Moreover, due the various histopathological changes in classification and stratification of mucinous lesions, including mucinous appendiceal adenocarcinomas, it is possible that the group of patients which is registered as having mucinous appendiceal adenocarcinomas in the NCR could be contaminated. Therefore, the pathological reports, including macroscopy and microscopy reports, of patients with appendiceal mucinous

adenocarcinomas with morphology codes 8470 and 8480, in which cystadenomas (8470/0), tumours of uncertain malignant potential (8480/1) and pseudomyxoma peritonei (8480/6) could be included, were retrospectively revised through a repeated linkage with PALGA. The histologic subtype was retrospectively changed for the patients concerned, according to the most recent histopathological classification for mucinous appendiceal neoplasms[27].

Aim and outline of the thesis

This thesis aims to provide insight into clinical and pathological aspects of small bowel and appendiceal cancer, by examining the epidemiology, clinical disease course, treatment and prognostic factors of these rare gastrointestinal cancers. The main objectives of the described studies in this thesis were:

- To obtain insight into the epidemiology of locoregional and metastatic small bowel cancer by studying the incidence, trends in treatment and overall survival (part I).
- To evaluate the use and effects of palliative systemic therapy in patients with metastatic small bowel cancer (part II).
- To assess the prognostic value of histologic subtype and its impact on treatment options and survival in patients with appendiceal cancer (part III).

Part I: Epidemiology of small bowel cancer

In chapter 2, the incidence, treatment and overall survival over time of patients with SBA is established, with emphasis on the location of the primary tumour and its relation to patient outcomes. In chapter 3, the incidence, risk factors and treatment-related survival is studied, in the subgroup of patients with peritoneal metastases of SBA, one of the most frequently encountered metastases in SBA.

Part II: Palliative systemic therapy in metastatic small bowel cancer

Part II of this thesis focuses on the use and effectiveness of palliative systemic therapy, defined as the administration of cytotoxic and/or targeted agents, in patients with metastatic SBA. The use and effects of palliative chemotherapy are evaluated in chapter 4, whereas the use and effectiveness of the addition of targeted therapy to palliative chemotherapy in patients with metastatic SBA is described in chapter 5.

Part III: Histologic subtype in appendiceal cancer

In part III of this thesis, the prognostic value of histologic subtype in appendiceal cancer is studied, with special attention to mucinous appendiceal neoplasms, using the recent international histopathological classification. In chapter 6, an overview of the differences in mucinous appendiceal neoplasms in terms of histologic subtype and its impact on

management of these tumours is provided. In chapter 7, the prognostic relevance of histologic subtype in a subset of patients with mucinous, non-mucinous and signet ring cell adenocarcinomas in both locoregional disease and metastatic disease of appendiceal adenocarcinoma is determined. Chapter 8 evaluated the differences in clinical course of disease in patients with metastatic mucinous appendiceal neoplasms and showed the importance to subdivide patients with mucinous appendiceal lesions according to the latest proposed consensus-based histopathological classification.

In chapter 9 of this thesis, a summary of the main findings, methodological considerations and implications for clinical practice and future research are outlined.

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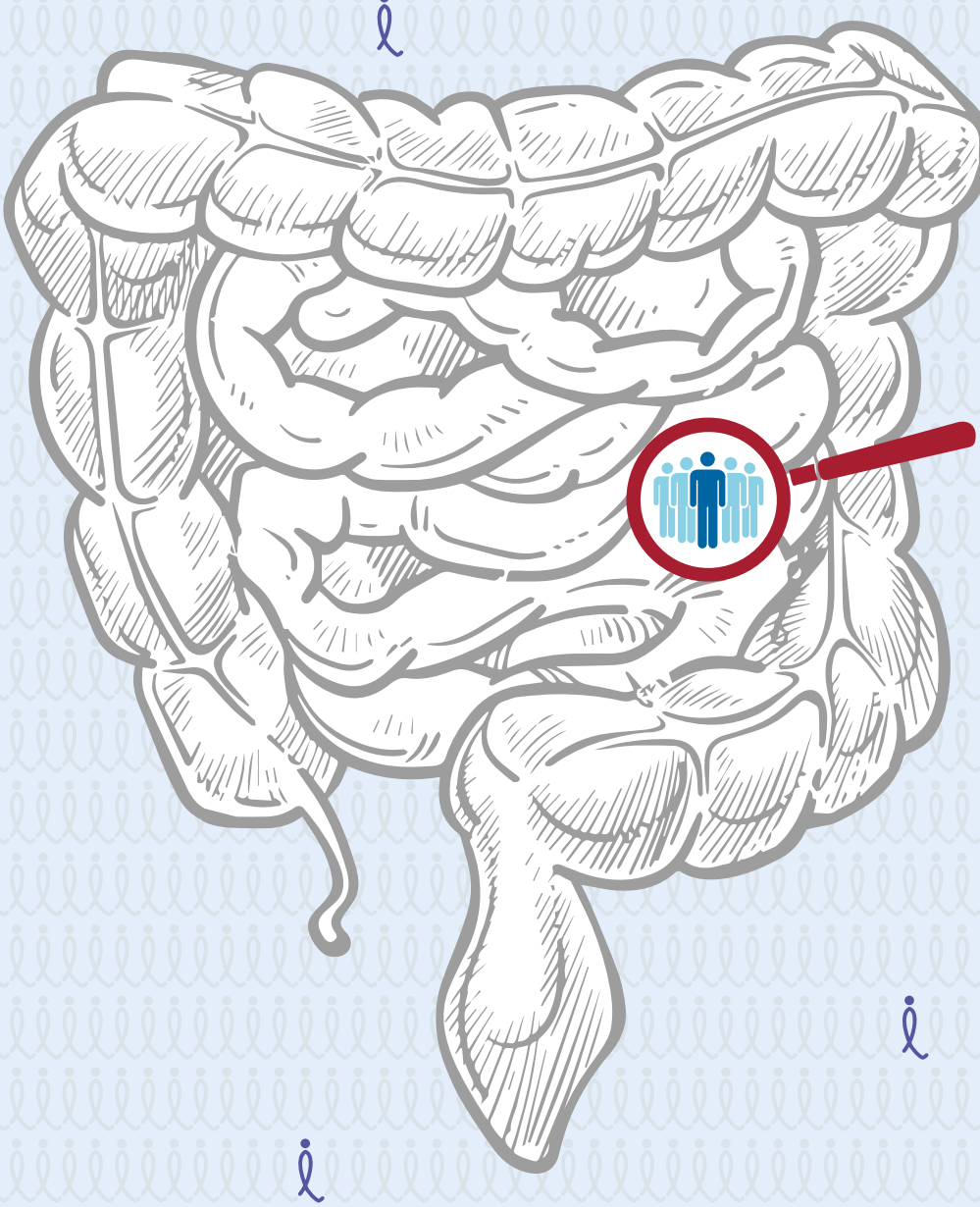
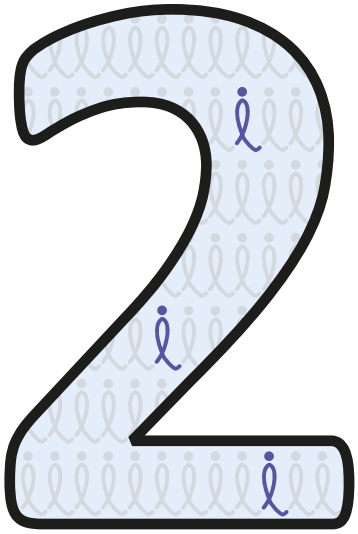
Part I

Epidemiology of small bowel cancer





Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013:

A population-based study in the Netherlands

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Abstract

Background: We conducted a population-based study to establish the incidence, treatment and overall survival over time of patients with small bowel adenocarcinoma.

Material and Methods: All patients diagnosed with small bowel adenocarcinoma in the Netherlands between 1999 and 2013 were included (n = 1775). Age-standardized incidence rates were calculated per 100.000 person-years using the European standardized population rate. The influence of patient and tumour characteristics on the administration of chemotherapy was analysed by means of a multivariable logistic regression analysis. The Cochran-Armitage trend test was conducted to evaluate trends in treatment and survival and the cox proportional hazards model was used to identify prognostic factors of overall survival.

Results: The incidence of small bowel adenocarcinomas increased, mainly due to an almost twofold increase of duodenal adenocarcinomas. Patients with locoregional duodenal tumours were less likely to undergo surgery (58%), towards 95% of the locoregional jejunal and ileal tumours ($p < 0.0001$). The use of chemotherapy doubled for adjuvant (7 to 15%) and palliative chemotherapy (19 to 37%). Overall survival of patients with locoregional disease increased from 19 to 34 months ($p = 0.0006$), whereas overall survival of patients with metastatic disease remained 4-5 months. Favourable prognostic factors for prolonged survival in locoregional disease, identified by multivariable survival analysis, included age <60 years, tumour stage I or II, diagnosis in 2009-2013, surgical treatment and chemotherapy. Favourable prognostic factors for prolonged survival in metastatic disease were age <50 years, jejunal tumours, surgical treatment and chemotherapy.

Conclusion: Small bowel adenocarcinomas are rare tumours with an increasing incidence. The administration of adjuvant and palliative chemotherapy doubled, but overall survival only increased for patients with locoregional disease. Given the rarity and dismal prognosis, it is important to develop international studies to determine the optimal treatment for these patients.

Introduction

Small bowel tumours are rare malignant tumours, accounting for less than 5% of all gastro-intestinal tumours, but the incidence is rising[1]. Small bowel tumours have an unequal distribution in the small bowel. The preferred location depends on the histological subtype. The four major subtypes of small bowel tumours are adenocarcinomas, neuroendocrine tumours (including carcinoids), gastro-intestinal stromal tumours (GIST) and lymphomas[2]. Adenocarcinomas and neuroendocrine tumours are the most common subtypes in the small bowel, both accounting for approximately 40% of small bowel tumours[3-5].

Patients with small bowel adenocarcinomas merely present with non-specific symptoms, such as vague abdominal pain, weight loss, nausea and vomiting, bowel obstruction, gastrointestinal bleeding or anaemia, which challenges the diagnosis. Known predisposing risk factors for these tumours are autoimmune disorders including celiac disease, Crohn's disease and several hereditary cancer syndromes, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC) and the Peutz-Jeghers syndrome. These predisposing genetic disorders also play a role in the pathogenesis of colon cancer. Although the precise pathogenesis of small bowel adenocarcinomas is unknown, most available data suggest a carcinoma sequence driven multistep process of specific genetic changes similar to colorectal cancers[5-9].

Due to the rarity of the disease, data about small bowel adenocarcinomas are scarce, diverse and contradictory. Therefore we conducted a population-based study to establish the incidence, treatment and overall survival over time of patients with a small bowel adenocarcinoma in the Netherlands between 1999 and 2013.

Material and Methods

Data collection

For this study, data were retrieved from the Netherlands Cancer Registry (NCR), which is managed by the Comprehensive Cancer Organisation the Netherlands. The nationwide NCR covers nearly 17 million inhabitants and comprises population-based data on all newly diagnosed malignancies. Primary source of notification of the NCR is the automated nationwide pathological archive (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses. Required information on diagnosis, treatment, patient- and tumour characteristics are routinely extracted from hospital medical records by specially trained registrars operating on behalf of the NCR.

Patients were included if they were diagnosed between 1999 and 2013 with an adenocarcinoma of the small bowel, according to the third version of the International Classification of Disease for Oncology (ICD-O) (topography code C17). Tumours were classified as adenocarcinomas with the following morphology codes: 8140, 8144, 8145, 8210, 8255, 8260, 8261, 8263, 8480, 8481, 8490, 8560, 8570, 8574. Patients with adenocarcinomas arising from a Meckel's diverticulum, as well as patients with neuroendocrine tumours, gastrointestinal stromal tumours, lymphomas or undifferentiated tumours in the small bowel were excluded from analysis.

All adenocarcinomas were classified according to the Tumour Lymph Node Metastasis (TNM) classification and were staged following the recommendations of the International Union Against Cancer in the respective period. The tumours were categorized in two groups, either as locoregional ($T_{1-4}N_{0-2}M_0$) or metastatic cancer ($T_{1-4}N_{0-2}M_1$).

Vital status of patients at 1 January 2014 was assessed through linkage with civil municipal registries and the central bureau for genealogy, which collects data on all deceased Dutch inhabitants. Survival was computed based on all-cause mortality.

Statistical analysis

Descriptive statistics were used to describe the patient and tumour characteristics. Differences in certain tumour characteristics and treatment between the locoregional and metastatic group were compared and analysed using a two-sided χ^2-test. To evaluate trends in treatment and survival, patients were first categorized in three groups by period of diagnosis (1999-2003, 2004-2008 and 2009-2013), and subsequently, trends between the subgroups were analysed by means of a Cochran-Armitage trend test.

Age-standardized incidence rates were calculated per 100.000 person-years using the

European standardized population rate (ESR) for the respective study period. Estimated annual percentage changes (EAPCs) in incidence were estimated by Poisson regression models. The independent influence of relevant patient and tumour characteristics on the administration of chemotherapy for patients with locoregional and metastatic disease was analysed by means of a multivariable logistic regression analysis.

Survival time was defined as the time from date of diagnosis to death. Patients who were lost to follow-up or still alive at 1 January 2014 were censored. Evaluation of significant differences of survival between the subgroups occurred by means of a log-rank test. Multivariable survival analyses, using the cox proportional hazards model, were carried out to identify independent prognostic factors of overall survival. In order to investigate the effect of therapy on the hazard ratios (HR) of dying, two separate multivariable models were run with and without treatment variables (surgery yes vs. no and chemotherapy yes vs. no).

The statistical package SAS Statistical software (version 9.4, SAS institute, Cary, NC, USA) was used to analyse the data. For all statistical tests, a two-sided p-value $p < 0.05$ was considered as statistically significant.

Results

A total of 3930 patients were diagnosed with a small bowel tumour between 1 January 1999 and 31 December 2013. The most common histological subtype was adenocarcinoma, accounting for 1775 cases (45%), followed by neuroendocrine tumours (1429 patients, 36%) and gastro-intestinal stromal tumours (529 patients, 13%). The 1775 patients diagnosed with an adenocarcinoma were enrolled in this study.

The patients' characteristics are summarized in table 1. We found an equal gender distribution, the median age at time of diagnosis was 69 (range 17-97). The tumours were mainly located in the duodenum (58%), and respectively 19% and 14% in the jejunum and the ileum.

The age-standardized incidence of small bowel adenocarcinomas increased from 0.5 per 100,000 inhabitants in 1999 to 0.7 per 100,000 inhabitants in 2013 with an estimated annual percentage change (EAPC) of 3.7% ($p < 0.001$). The increased incidence of small bowel adenocarcinomas is mainly caused by a twofold increase of duodenal adenocarcinomas from 233 in 1999-2003 to 478 cases in 2009-2013 ($p = 0.013$) (figure 1).

Thirty-three percent of the patients had metastatic disease. Over time the proportion of patients presenting with metastatic disease increased from 27% in 1999-2003 to 38% in 2009-2013 ($p < 0.0001$). Moreover, the percentage of patients presenting with metastases in multiple organs increased as well from 8% in 1999-2003 to 28% in 2009-2013 ($p = 0.0003$). The most common metastatic site was the liver (46%), followed by the peritoneal cavity (29%) and extra regional lymph nodes (12%). Patients with metastatic disease arising from duodenal origin showed a different metastatic pattern compared to patients with primary tumours located elsewhere in the small bowel. The majority of patients with metastatic duodenal adenocarcinomas had metastases located in the liver (54%), whereas in patients with metastases from non-duodenal adenocarcinomas the peritoneal cavity was the most frequently affected site (44%).

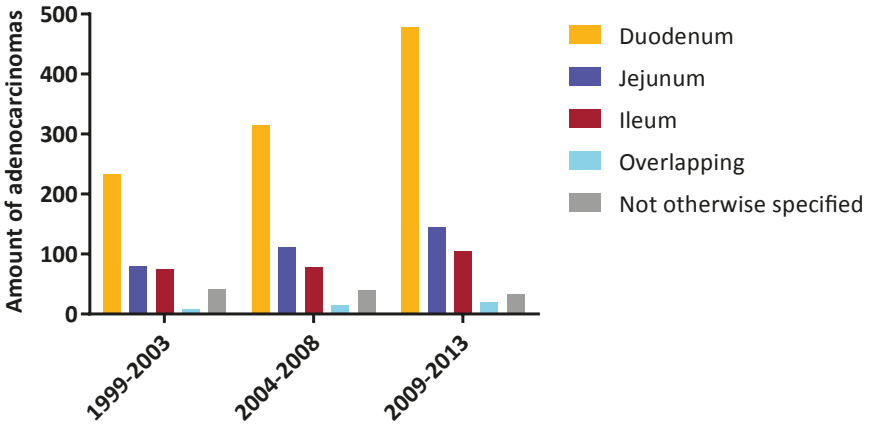
In the group of patients with locoregional disease, 73% underwent a surgical resection of the primary tumour in contrast to 30% of the patients with metastatic disease ($p < 0.0001$). The percentage of patients with locoregional disease undergoing a resection slightly increased from 71% in 1999-2003 to 77% in 2009-2013, while the percentage of patients with metastatic disease undergoing a surgical resection of the primary tumour decreased from 38% to 25% ($p = 0.0031$).

Table 1. Characteristics of patients diagnosed with a small bowel adenocarcinoma, by primary tumour localization (n = 1775).

	Total N (%)	**Duodenum N (%)**	**Non-Duodenum N (%)**	***p*-value**
Sex				0.1343
Male	909 (51.2)	541 (52.7)	368 (49.1)	
Female	866 (48.8)	485 (47.3)	381 (50.9)	
Age (years)				0.0028
< 50	178 (10.0)	84 (8.2)	94 (12.6)	
50-59	281 (15.8)	155 (15.1)	126 (16.8)	
60-69	458 (25.8)	257 (25.1)	201 (26.8)	
70-79	509 (28.7)	307 (29.9)	202 (27.0)	
≥ 80	349 (19.7)	223 (21.7)	126 (16.8)	
Location primary tumour				n.a.
Duodenum	1026 (57.8)	1026 (100.0)	Not applicable	
Jejunum	336 (18.9)	Not applicable	336 (44.9)	
Ileum	257 (14.5)	Not applicable	257 (34.3)	
Overlapping	42 (2.4)	Not applicable	42 (5.6)	
Unknown/NOS	114 (6.4)	Not applicable	114 (15.2)	
TNM stage group				< 0.0001
I	115 (6.5)	66 (6.4)	49 (6.5)	
II	501 (28.2)	219 (21.4)	282 (37.7)	
III	419 (23.6)	257 (25.1)	162 (21.6)	
IV	581 (32.7)	352 (34.3)	229 (30.6)	
X	159 (9.0)	132 (12.9)	27 (3.6)	
Number of metastatic sites				0.0092
1	447 (76.9)	286 (81.3)	161 (70.3)	
2	97 (16.7)	48 (13.6)	49 (21.4)	
≥ 3	37 (6.4)	18 (5.1)	19 (8.3)	
Period of diagnosis				0.0207
1999-2003	436 (24.6)	233 (22.7)	203 (27.1)	
2004-2008	559 (31.5)	315 (30.7)	244 (32.6)	
2009-2013	780 (43.9)	478 (46.6)	302 (40.3)	
Surgery				< 0.0001
Yes	1045 (58.9)	418 (40.7)	627 (83.7)	
No	730 (41.1)	608 (59.3)	122 (16.3)	
Chemotherapy				0.0103
Yes	321 (18.1)	165 (16.1)	156 (20.8)	
No	1454 (81.9)	861 (83.9)	593 (79.2)	
Total	1775	1026	749	

NOS = not otherwise specified

Figure 1: Primary tumour location within the small bowel for patients diagnosed with a small bowel adenocarcinoma between 1999 and 2013 in the Netherlands according to period of diagnosis (n = 1775).



Tumour location was an important predictive factor for surgery. In locoregional disease, 58% of the patients with duodenal carcinomas underwent a surgical intervention with curative intent as compared to 95% of the patients with jejunal and ileal carcinomas ($p < 0.0001$). The percentage of patients with duodenal adenocarcinomas undergoing surgery increased from 54% to 64% throughout the study period ($p = 0.0179$). In metastatic disease, only 7% of the patients with duodenal adenocarcinomas underwent surgery, in contrast to respectively 63% and 81% of the patients with jejunal and ileal tumours ($p < 0.0001$). Other palliative interventions, such as a bilio-digestive or intestinal bypass, endoscopic stent placement or celiac plexus block, were performed in 24% of the patients with metastatic duodenal adenocarcinomas, and respectively in 5% and 6% of the patients with metastatic jejunal and ileal tumours. In addition, 14% of the patients with locoregional duodenal adenocarcinomas received a palliative intervention.

Eleven percent of the patients with locoregional disease received chemotherapy, while 33% of the patients with metastatic disease did. The use of chemotherapy increased over time for patients with locoregional disease from 7% in 1999-2003 to 15% in 2009-2013 ($p = 0.0001$). Of the 91 patients with locoregional disease, undergoing both surgical resection and chemotherapy, the majority received the chemotherapy in the adjuvant setting. Multivariable logistic regression analyses showed that chemotherapy in patients with locoregional disease was more often offered to younger patients, patients with ileal or stage III tumours or patients who were diagnosed in the period 2009-2013 (table 2). In patients with metastatic disease the prescription of palliative chemotherapy significantly

increased from 19% in 1999-2003 to 37% in 2009-2013 (p = 0.001). In metastatic disease, younger patients and patients who were diagnosed after 2003 received chemotherapy more frequently (table 2).

Table 2. Crude percentages and adjusted odds for receiving chemotherapy among patients diagnosed with small bowel adenocarcinomas between 1999 and 2013 in the Netherlands (n = 1775).

	Locoregional disease (n = 1194)		Metastatic disease (n = 581)	
	Crude percentage (%)	Odds ratios (95% CI)	Crude percentage (%)	Odds ratios (95% CI)
Sex				
Male	12.1	1.00 (reference)	31.0	1.00 (reference)
Female	9.9	0.85 (0.57-1.27)	34.0	1.18 (0.80-1.73)
Age (years)				
< 50	25.9	2.16 (1.22-3.81)	56.5	1.99 (1.08-3.67)
50-59	18.9	1.54 (0.92-2.59)	51.1	1.63 (0.95-2.78)
60-69	16.0	1.00 (reference)	39.4	1.00 (reference)
70-79	5.6	0.34 (0.19-0.61)	23.7	0.48 (0.29-0.78)
≥ 80	0.0	Not applicable	3.2	0.05 (0.02-0.16)
Location primary tumour				
Duodenum	9.5	1.00 (reference)	28.7	1.00 (reference)
Jejunum	13.0	1.61 (0.97-2.68)	43.3	1.49 (0.90-2.48)
Ileum	15.1	2.00 (1.16-3.47)	34.7	1.16 (0.64-2.12)
Overlapping	8.3	1.03 (0.21-5.02)	38.9	1.11 (0.40-3.06)
Unknown/NOS	9.7	1.28 (0.52-3.16)	33.3	1.33 (0.61-2.86)
TNM stage group				
I	0.0	Not applicable	Not included in the analysis	
II	7.6	1.00 (reference)		
III	20.8	3.45 (2.22-5.35)		
X	4.4	1.89 (0.77-4.66)		
Period of diagnosis				
1999-2003	6.6	1.00 (reference)	18.6	1.00 (reference)
2004-2008	9.8	1.74 (0.96-3.16)	34.7	2.31 (1.27-4.19)
2009-2013	15.0	3.10 (1.79-5.38)	36.9	3.00 (1.72-5.26)

NOS = not otherwise specified

The median overall survival of patients diagnosed with a small bowel adenocarcinoma remained stable around 13-14 months, with one and five year survival rates of 53% and 25% respectively. Patients with locoregional disease had a median overall survival of 25 months (one and five year survival rates 65% and 36% respectively). The median overall survival of patients with locoregional disease increased from 19 months in the first period to 34 months in the last period (p = 0.0006). In patients with locoregional disease who underwent a surgical resection, an overall survival of 48 months was observed. Whereas patients receiving (neo-)adjuvant chemotherapy in combination with surgery exhibited a

significantly better overall survival of 66 months (p = 0.0338).

The median overall survival of patients with metastatic disease remained stable around 4-5 months (one and five year survival rates 26% and 3% respectively). A median overall survival of 10 months was seen in patients with metastatic disease who were treated with palliative chemotherapy, in contrast to a 3 month median overall survival in patients who did not receive palliative chemotherapy.

Favourable prognostic factors, identified by a separate multivariable survival analysis, including patients with locoregional disease, were age < 60 years, low tumour stage (stage I, II) and diagnosis in the period 2009-2013 (table 3). Factors that were associated with poor survival included age ≥70 years, tumour localization in the duodenum and an unknown tumour stage (stage X). Surgical treatment and chemotherapy, were added separately to the model to investigate its effect on the hazard ratio of death according to period of diagnosis and different patient and tumour characteristics. Surgical treatment and chemotherapy were both favourable prognostic factors. Remarkably, after adjustment for surgery only, a tumour located in the duodenum was no longer a negative prognostic factor and diagnosis in the period 2004-2008 became a positive prognostic factor. Chemotherapy did not influence the effect of the other characteristics on the hazard ratio of death.

In a multivariable survival analysis without adjustment for treatment including patients with metastatic disease, age <50 years and primary tumour located in the jejunum or ileum were positive prognostic factors (table 4). Age ≥80 years was the only negative prognostic factor. No beneficial influence of time was seen. After adjustment for chemotherapy and surgery, both positive prognostic factors, a primary tumour located in the ileum became a negative prognostic factor.

Table 3. Crude median overall survival, crude 1-year survival, adjusted hazard ratios with and without adjustment for treatment for patients diagnosed with locoregional small bowel adenocarcinoma between 1999 and 2013 in the Netherlands (n = 1194).

	Crude median overall survival (months)	Crude 1-year survival (%)	Multivariate HR (95% CI) [a]	Multivariate HR (95% CI) adjusted for treatment [a]
Sex				
Male	26.1	65.8	1.00 (reference)	1.00 (reference)
Female	24.5	64.7	0.87 (0.75-1.00)	0.82 (0.71-0.95)
Age (years)				
< 50	73.0	84.9	0.61 (0.44-0.83)	0.66 (0.48-0.91)
50-59	66.4	79.8	0.66 (0.51-0.86)	0.68 (0.53-0.89)
60-69	32.4	72.1	1.00 (reference)	1.00 (reference)
70-79	21.9	62.8	1.34 (1.09-1.64)	1.21 (0.98-1.48)
≥ 80	7.9	40.9	2.18 (1.76-2.71)	1.52 (1.21-1.90)
Location primary tumour				
Duodenum	16.3	57.8	1.00 (reference)	1.00 (reference)
Jejunum	62.6	81.9	0.62 (0.51-0.77)	0.93 (0.74-1.16)
Ileum	40.2	73.3	0.79 (0.63-0.98)	1.22 (0.97-1.54)
Overlapping	41.3	79.1	0.76 (0.45-1.29)	0.97 (0.58-1.65)
Unknown/NOS	22.6	55.5	0.75 (0.55-1.02)	1.12 (0.82-1.54)
TNM stage group				
I	77.2	84.8	0.39 (0.29-0.53)	0.42 (0.31-0.56)
II	42.7	73.4	0.65 (0.55-0.77)	0.63 (0.53-0.75)
III	20.5	65.0	1.00 (reference)	1.00 (reference)
X	4.7	26.4	1.73 (1.39-2.17)	0.85 (0.67-1.07)
Period of diagnosis				
1999-2003	18.5	61.3	1.00 (reference)	1.00 (reference)
2004-2008	23.1	63.7	0.87 (0.73-1.03)	0.84 (0.70-0.99)
2009-2013	34.1	69.4	0.68 (0.56-0.81)	0.74 (0.61-0.89)
Surgery				
Yes	50.3	79.8	Not included	0.23 (0.18-0.28)
No	5.6	73.6	in the analysis	1.00 (reference)
Chemotherapy				
Yes	35.5	84.3	Not included	0.55 (0.41-0.73)
No	23.5	63.0	in the analysis	1.00 (reference)

NOS = not otherwise specified; [a] adjusted for all variables listed

Table 4. Crude median overall survival, crude 1-year survival, adjusted hazard ratios with and without adjustment for treatment for patients diagnosed with metastatic small bowel adenocarcinoma between 1999 and 2013 in the Netherlands (n = 581).

	Crude median overall survival (months)	Crude 1-year survival (%)	Multivariate HR (95% CI) [a]	Multivariate HR (95% CI) adjusted for treatment [a]
Sex				
Male	4.5	21.2	1.00 (reference)	1.00 (reference)
Female	5.1	30.5	0.89 (0.75-1.06)	0.90 (0.75-1.07)
Age (years)				
< 50	8.3	38.7	0.69 (0.50-0.95)	0.79 (0.57-1.08)
50-59	5.7	31.0	0.97 (0.73-1.27)	1.00 (0.76-1.32)
60-69	5.2	28.9	1.00 (reference)	1.00 (reference)
70-79	4.7	23.1	1.16 (0.93-1.46)	1.02 (0.81-1.29)
≥ 80	2.4	12.2	1.64 (1.26-2.15)	1.21 (0.91-1.60)
Location primary tumour				
Duodenum	4.0	19.2	1.00 (reference)	1.00 (reference)
Jejunum	9.7	40.5	0.54 (0.42-0.70)	0.90 (0.68-1.18)
Ileum	5.0	29.9	0.74 (0.56-0.97)	1.57 (1.13-2.17)
Overlapping	4.9	29.6	0.83 (0.51-1.36)	1.19 (0.72-1.97)
Unknown/NOS	5.7	39.1	0.79 (0.56-1.12)	1.48 (1.03-2.15)
Period of diagnosis				
1999-2003	4.5	27.1	1.00 (reference)	1.00 (reference)
2004-2008	4.8	27.7	0.92 (0.72-1.17)	1.10 (0.86-1.41)
2009-2013	5.2	23.9	0.95 (0.76-1.20)	1.12 (0.89-1.42)
Surgery				
Yes	10.6	47.2	Not included	0.38 (0.30-0.50)
No	3.9	16.6	in the analysis	1.00 (reference)
Chemotherapy				
Yes	10.5	43.4	Not included	0.50 (0.40-0.61)
No	3.2	17.5	in the analysis	1.00 (reference)

NOS = not otherwise specified, [a] adjusted for all variables listed

Discussion

This population-based study examined the incidence, treatment and overall survival over time in patients diagnosed with a small bowel adenocarcinoma in the Netherlands between 1999 and 2013 and is one of the largest conducted studies in the field of small bowel adenocarcinomas so far. Our study showed that the incidence of small bowel adenocarcinomas is rising. Furthermore, we found that the resection rates in non-metastatic small bowel cancer increased and the overall survival in patients with locoregional disease improved over time. The overall survival of patients with metastatic disease remained stable, despite the increased treatment with palliative chemotherapy.

The distribution pattern of small bowel adenocarcinomas throughout the bowel was comparable with previous studies[3-5, 7]. It has been hypothesized that the duodenum might be more susceptible for carcinogenesis than the jejunum and ileum due to the metabolism or dilution of ingested carcinogens in transit through the small bowel or interactions of the carcinogens with the pancreaticobiliary secretions[3, 7, 10, 11].

Based on our comparison between patients diagnosed with tumours located in the duodenum versus patients diagnosed with tumours located elsewhere in the small bowel, it could be questioned whether these tumours should be considered as one entity. Patients with tumours located in the duodenum are often slightly older, have more advanced disease and have a different metastatic pattern.

A slight increase in the incidence of small bowel adenocarcinomas was seen between 1999 and 2013, which is mainly caused by the twofold increase of duodenal adenocarcinomas. The exact cause for the specific increase in duodenal adenocarcinomas is unknown. Partially it can be explained by improved diagnostics, resulting in a reduction of misclassification of duodenal adenocarcinomas as pancreatic tumours and adenocarcinoma of unknown primary (ACUP)[10, 12]. The modified food consumption might have attributed to increased incidence rates as well. Previous studies found sugar, refined carbohydrates, red meat and smoked food to be associated with the development of small bowel adenocarcinomas[2, 11].

The percentage of patients diagnosed with metastatic disease increased over time, which can be explained by stage migration caused by new and improved diagnostics, such as multidetector row computed tomography scans (MDCT) and magnetic resonance (MR) enteroclysis[13].

Surgical resection is the only therapy for potential cure in small bowel adenocarcinoma[2]. In line with previous studies, 73% of the patients with locoregional disease underwent an

intentionally curative resection[5, 7]. Resection rates were higher in jejunal and ileal tumours compared to resection rates in duodenal tumours, since surgical resection of upper duodenal tumours requires a pancreaticoduodenectomy, which is specialized major surgery in comparison to the more simple segmental resections with removal of surrounding tissue for jejunal and ileal tumours[5, 7].

Over time the resection rates increased, especially due to an increased number of resections in patients with duodenal tumours. We hypothesize that may be due to the centralization of pancreaticoduodenectomies in the Netherlands[14, 15]. The amount of surgical interventions in patients with metastatic disease decreased drastically, which is probably the result of improved palliative interventions, such as endoscopically placed (bilio-)duodenal endoprotheses, and the increased use of chemotherapy[16]. Palliative interventions in patients with non-metastatic small bowel cancer were mostly performed in patients with duodenal adenocarcinomas, which are more often irresectable compared to jejunal and ileal tumours[7].

The proportion of patients receiving chemotherapy doubled during the study period, both for patients with locoregional and metastatic disease. Especially in patients with locoregional disease the twofold increase is remarkable, since non-observational studies addressing the beneficial effect of chemotherapy are lacking. Overman et al found adjuvant chemotherapy to be associated with an improvement of disease free survival, but not with improvement of overall survival[17]. Recently, a population-based study conducted by Ecker et al showed a survival benefit of 16 months (42 vs 26 months) for patients with stage III tumours treated with adjuvant chemotherapy[18]. We demonstrate that in patients with locoregional disease chemotherapy was more often offered to younger patients, patients with ileal or stage III tumours and patients who were diagnosed in the period 2009-2013. In metastatic disease however, the doubling of palliative chemotherapy is not surprising, since a survival benefit of several months has already been observed in multiple retrospective studies[5, 19-21]. In patients with metastatic disease, only a younger age and diagnosis after 2003 were positive predictive factors for receiving palliative chemotherapy.

The overall survival rate of all patients with an adenocarcinoma of the small bowel did not improve over time and remained dismal with an overall median survival of 13-14 months. Our results are inferior to the reported overall survival of approximately 20 months in other population-based studies, but these studies were merely conducted before the millennium and might have included neuroendocrine tumours with a more indolent behaviour[5, 7, 22, 23].

The median overall survival of patients with locoregional disease improved from 19 months in 1999-2003 to 34 months in 2009-2013, which might be explained by stage migration, increased

use of chemotherapy and the centralization of pancreatic cancer surgery. Moreover, we found that patients treated with adjuvant chemotherapy after surgical resection had significant higher survival rates, 66 months compared to 48 months for patients not treated with adjuvant chemotherapy. However, it should be noted that the amount of patients receiving both treatments were limited in our study. Other favourable prognostic factors for prolonged survival in patients with locoregional disease, identified by multivariable analysis, were age <60 years, tumour stage I and II, surgical treatment and chemotherapy. These findings are comparable to previously determined prognostic factors[3, 5, 7, 20, 22, 24]. In addition, in patients with locoregional disease, duodenal tumours appeared to be an adverse prognostic factor in multivariable analysis without adjustment for treatment. However, after adjustment for surgery only, a duodenal tumour was not a negative prognostic factor anymore, which implies that the poor prognosis of these tumours is the result of the relative lack of possibilities for surgical intervention.

In metastatic disease the overall survival remained stable around 4-5 months despite doubling of the prescription of palliative chemotherapy from 19% to 37% in the recent years. In patients with metastatic disease, favourable prognostic factors identified by multivariable analysis included age <50 years, primary tumour located in the jejunum, surgical treatment and chemotherapy. These prognostic factors are also consistent to previously published data[3, 7, 22].

A limitation of our study is that detailed information on performance status, nutritional status, disease related symptoms, the specific tumour localization within the duodenum, type of chemotherapy and type of surgical and palliative intervention are lacking, due to the population based nature of our data. However, our results did not differ from other studies[3-5, 7].

In conclusion, small bowel adenocarcinomas are rare tumours with an increasing incidence, mainly caused by the rise of duodenal adenocarcinomas. The median overall survival of patients with locoregional disease improved significantly over time, which might be due to the increasing use of chemotherapy and the implementation of centralizing pancreatic cancer surgery. However, the overall survival of patients with metastatic disease remained stable, despite doubling the administration of palliative chemotherapy. Due to the rarity and dismal prognosis of this disease, it is of importance to develop international studies to determine the optimal treatment for these patients. The differences found in characteristics and median overall survival between patients diagnosed with tumours located in the duodenum and tumours located elsewhere in the small bowel might suggest that in future research both should be considered as different entities.

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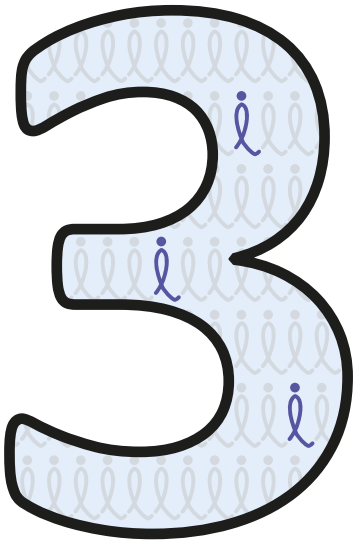

Synchronous peritoneal metastases of small bowel adenocarcinoma:

Insights into an underexposed clinical phenomenon

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Abstract

Background: The aim of this population-based study was to provide insight into the incidence, risk factors and treatment-related survival of patients with peritoneal metastases (PM) of small bowel adenocarcinoma (SBA).

Methods: Data from the Netherlands Cancer Registry were used. All patients diagnosed with SBA between 2005 and 2014 were included. The influence of patient and tumour characteristics on the odds of developing PM was analysed. Subsequently, for all further analyses, patients without synchronous PM of SBA were excluded. The log-rank test and Kaplan-Meier analyses were conducted to estimate survival, and the Cox proportional hazards model was used to evaluate the risk of death.

Results: Of the 1428 included patients diagnosed with SBA, 181 (13%) presented with synchronous PM. Synchronous PM was found in 9% of the duodenal tumours and in 17% of the more distal tumours. Median overall survival of all patients with PM was 5.9 months, whereas survival of both 11 months was observed in patients treated with primary tumour resection or palliative chemotherapy and 32 months after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC). Poor prognostic factors for survival were age ≥70 years (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.1-2.2), systemic metastases other than PM (HR 2.0, 95% CI 1.4-2.9) and an advanced (HR 1.9, 95% CI 1.3-3.0) or unknown T-stage (HR 2.1, 95% CI 1.2-3.5).

Conclusions: Synchronous PM was frequently encountered in SBA. Without treatment, prognosis was extremely poor. Survival was higher after primary tumour resection, palliative chemotherapy and CRS+HIPEC, but selection bias probably played a significant role calling for further clinical research.

Introduction

One of the most frequently affected metastatic sites in patients with small bowel adenocarcinoma (SBA) is the peritoneal cavity, especially in tumours arising from the jejunum and ileum[1-3]. Other common metastatic sites of SBA include the liver and extra-regional lymph nodes. The prognosis of metastatic SBA is poor with a median overall survival of 4-5 months and 5-year survival rates of 3-5%[1, 2, 4, 5]. Data on survival according to metastatic site in patients with a primary SBA are absent, and as a result, specific information on survival of patients with peritoneal metastases (PM) is unknown.

In gastro-intestinal malignancies, PM is usually regarded as a virtually untreatable condition, mainly because of the poor response to conventional types of therapy, such as systemic therapy, surgical resection or radiation[3, 6-10]. Since the introduction of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) more than two decades ago, major improvements in overall survival have been achieved in patients with pseudomyxoma peritonei and PM of colorectal cancer (CRC)[6, 11-13]. Owing to similarities between SBA and CRC, it is thought that CRS+HIPEC might also benefit patients with PM of SBA[4, 14]. Some small studies already showed the potential beneficial effect of CRS+HIPEC in small groups of selected patients with PM of SBA, but prospective studies are lacking[6, 7].

Currently, data about PM of SBA are virtually absent. Since these data are of importance to patients suffering from this condition and physicians treating it, we performed a population-based study to establish incidence, risk factors and overall survival of patients with synchronous PM of SBA in the Netherlands between 2005-2014.

Materials and Methods

Data collection

Data were retrieved from the Netherlands Cancer Registry (NCR). The NCR covers nearly 17 million inhabitants of the Netherlands and comprises population-based data on all newly diagnosed malignancies of all Dutch citizens. Primary source of notification of the NCR is the automated nationwide pathological archive (PALGA), supplemented with data from the national registry of hospital discharge diagnoses. The NCR comprises information on patient and tumour characteristics, diagnosis and treatment, which is routinely extracted from medical records by specially trained registrars operating on behalf of the NCR. In the databases of the NCR, the stage of the primary tumour is established according to the tumour-node-metastasis (TNM) classification. In case of missing pathological data, the clinical TNM stage is used. The anatomical site of the tumour and metastases are registered according to the third version of the International Classification of Disease for Oncology (ICD-O).

Patients diagnosed with SBA (ICD-O code C17) between 2005 and 2014 were included in this study and analysed for synchronous PM (C48). Synchronous metastases were defined as metastases diagnosed within 3 months after the initial SBA diagnosis. Tumours were classified as adenocarcinomas with the following morphology codes: 8140, 8144, 8145, 8210, 8255, 8260, 8261, 8263, 8480, 8481, 8490, 8560, 8570 and 8574. Patients were excluded if they were diagnosed with neuro-endocrine tumours, including carcinoids, gastro-intestinal stromal tumours or undifferentiated tumours or if they were newly diagnosed during autopsy.

The following treatment modalities were included in the study: palliative chemotherapy, palliative primary tumour resection and CRS+HIPEC. Palliative chemotherapy was defined as the administration of cytotoxic drugs or targeted agents. CRS+HIPEC was performed according to a nationwide Dutch protocol.

Vital status of patients was assessed on 1 February 2016 through linkage of the NCR with civil municipal registries and the central bureau for genealogy, which collects data on all deceased inhabitants of the Netherlands. Survival was computed on all-cause mortality.

Statistical analysis

Age-standardized incidence rates were calculated per 100,000 person-years using the European standardized population rate for the respective study period. Differences in patient and tumour characteristics were analysed with a two-sided chi-square test or Fisher's exact test in case of small samples. Trends between the two periods (2005-2009

and 2010-2014) were evaluated by means of a Cochran-Armitage trend test. The influence of independent patient and tumour characteristics on the odds of developing PM was analysed in a multivariable logistic regression analysis, and the 95% confidence interval (CI) was assessed.

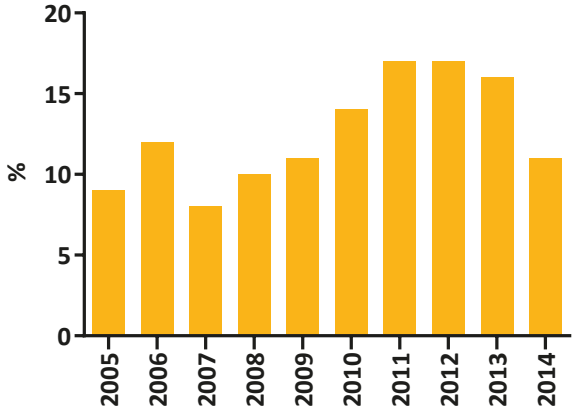
Survival time was defined as the time from the date of diagnosis until death or until the last follow-up date for patients who were lost to follow-up or who were still alive on 1 February 2016. Survival was estimated with the log-rank test and Kaplan-Meier analyses. For all possible prognostic factors of overall survival, univariable survival analyses were performed, using the Cox proportional hazards model. If univariable analyses tended towards statistical significance ($p < 0.10$), the risk of death corrected for these potential prognostic factors was subsequently evaluated with multivariable survival analyses. Hazard ratios (HRs) were presented with 95% CIs.

Data were analysed with the statistical package SAS Statistical Software, version 9.4 (SAS Institute, Cary, NC, USA). For all statistical tests, a two-sided p-value of $p < 0.05$ was considered as statistically significant.

Results

The present study included 1428 patients diagnosed with an SBA between 2005 and 2014, 181 of whom presented with synchronous PM (13%). According to topographical subtype, most patients with PM had a primary tumour in the duodenum (44%). Synchronous PM was found in 9% of the patients with a primary duodenal tumour, compared with 17% of the patients with a more distal tumour. Throughout the study period, the percentage of patients presenting with synchronous PM increased from 10% to 15% (figure 1). In duodenal tumours, this percentage increased from 8% to 10% ($p = 0.22$), and in non-duodenal tumours, it increased from 13% to 22% ($p < 0.01$). The age-standardized incidence of PM from SBA could not be calculated, as the incidence rate was below 0.1 per 100,000 inhabitants.

Figure 1. The percentage of patients presenting with synchronous peritoneal metastases (PM) in small bowel adenocarcinoma (SBA) in the Netherlands between 2005 and 2014, plotted against the total number of patients with a primary SBA per year.



In 62% of the PM of SBA patients, the peritoneal cavity was the only affected metastatic site. The most commonly affected metastatic sites besides the peritoneal cavity were the liver (59%), extra-regional lymph nodes (24%) and lungs (16%). Sex was distributed equally, and a median age of 66 years was found. Further details on patient and tumour characteristics are listed in table 1. In comparison to all patients with an SBA, patients with PM of SBA were younger, more often had a primary non-duodenal tumour, more often had an advanced T- and N-stage and were more often diagnosed in the period from 2010 to 2014. Primary tumour surgery was performed less often, whereas palliative chemotherapy was administered more frequently in the group of PM patients than in the overall group of SBA patients. All details on the differences between these groups are shown in table 2.

Table 1. General characteristics of patients diagnosed with PM of SBA in the Netherlands between 2005 and 2014, stratified for primary tumour location (n = 181)

	Total (n = 181)		**Duodenum (n = 80)**		**Non-duodenum (n = 101)**		***p*-value**
	N	(%)	N	(%)	N	(%)	
Sex							0.37
Male	85	(47)	41	(51)	44	(44)	
Female	96	(53)	39	(49)	57	(56)	
Age (years)							0.36
< 70	109	(60)	45	(56)	64	(63)	
≥ 70	72	(40)	35	(44)	37	(37)	
Location of primary tumour							n.a.
Duodenum	80	(44)	80	(100)	0	(0.0)	
Jejunum	40	(22)	0	(0)	40	(40)	
Ileum	41	(23)	0	(0)	41	(41)	
NOS	20	(11)	0	(0)	20	(20)	
T-stage							< 0.0001
T1-3	45	(25)	11	(14)	34	(34)	
T4	86	(48)	34	(43)	52	(51)	
Tx	50	(28)	35	(44)	15	(15)	
N-stage							0.18
N0	43	(24)	20	(25)	23	(23)	
N+	81	(45)	30	(38)	51	(51)	
Nx	57	(31)	30	(38)	27	(27)	
Metastases							0.53
PM only	113	(62)	52	(65)	61	(60)	
PM + other metastases	68	(38)	28	(35)	40	(40)	
Period							0.93
2005-2009	65	(36)	29	(36)	36	(36)	
2010-2014	116	(64)	51	(64)	65	(64)	
Primary tumour surgery							< 0.0001
Yes	77	(43)	8	(10)	69	(68)	
No	104	(57)	72	(90)	32	(32)	
Palliative chemotherapy							< 0.01
Yes	57	(31)	16	(20)	41	(41)	
No	124	(69)	64	(80)	60	(59)	
CRS+HIPEC							0.01
Yes	15	(8)	2	(3)	13	(13)	
No	166	(92)	78	(98)	88	(87)	

NOS = not otherwise specified; PM = peritoneal metastases; CRS+HIPEC = cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; SBA = small bowel adenocarcinoma.

Table 2. Comparison of general characteristics of patients with PM of SBA and of all patients with an SBA in the Netherlands between 2005 and 2014.

	PM of SBA		All SBA	
	N	(%)	N	(%)
Sex				
Male	85	(47)	722	(51)
Female	96	(53)	706	(49)
Age (years)				
< 70	109	(60)	739	(52)
≥ 70	72	(40)	689	(48)
Location of primary tumour				
Duodenum	80	(44)	856	(60)
Jejunum	40	(22)	263	(18)
Ileum	41	(23)	202	(14)
NOS	20	(11)	107	(7)
T-stage				
T1-3	45	(25)	546	(38)
T4	86	(48)	527	(37)
Tx	50	(28)	355	(25)
N-stage				
N0	43	(24)	563	(39)
N+	81	(45)	592	(41)
Nx	57	(31)	273	(19)
Period				
2005-2009	65	(36)	648	(45)
2010-2014	116	(64)	780	(55)
Primary tumour surgery				
Yes	77	(43)	811	(57)
No	104	(57)	617	(43)
Palliative chemotherapy				
Yes	57	(31)	318	(22)
No	124	(69)	1110	(78)
CRS+HIPEC				
Yes	15	(8)	15	(1)
No	166	(92)	1413	(99)
Total	181	(100)	1428	(100)

NOS = not otherwise specified; PM = peritoneal metastases; CRS+HIPEC = cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; SBA = small bowel adenocarcinoma.

Resection of the primary tumour was performed in 43% of the PM patients. This was significantly more often the case in patients with non-duodenal tumours than in patients with duodenal tumours, 69% versus 10% ($p < 0.0001$). Over time, no significant differences were seen in primary tumour resection.

In this 10-year period, 15 patients underwent CRS+HIPEC (8%). Of these patients, two had with PM of duodenal origin, whereas 13 patients had PM of non-duodenal tumours

(p = 0.01). In comparison to all SBA patients with PM, patients who underwent CRS+HIPEC were significantly younger with a median age of 53 years (p < 0.01) and more often had a primary tumour with a low T- and N-stage. Almost half of all procedures were performed in one hospital. Of the 15 patients receiving CRS+HIPEC, five underwent CRS+HIPEC in 2014, but no significant differences over time could be noted in the administration of CRS+HIPEC.

Palliative chemotherapy was administered in 31% of the patients with PM. It was twice more commonly prescribed to patients with a primary non-duodenal tumour (41%) than to patients with a primary duodenal tumour (20%) (p < 0.01). Palliative chemotherapy was given more frequently to patients younger than 70 years than to patients older than 70 years (p = 0.02). No significant differences between the two periods were found in the prescription of systemic therapy.

Multivariable logistic regression showed that higher odds ratios of developing PM were associated with a primary tumour distal to the duodenum, an advanced or unknown T- and N-stage and diagnosis in the last period 2010-2014, whereas lower odds ratios were associated with age ≥70 years (table 3).

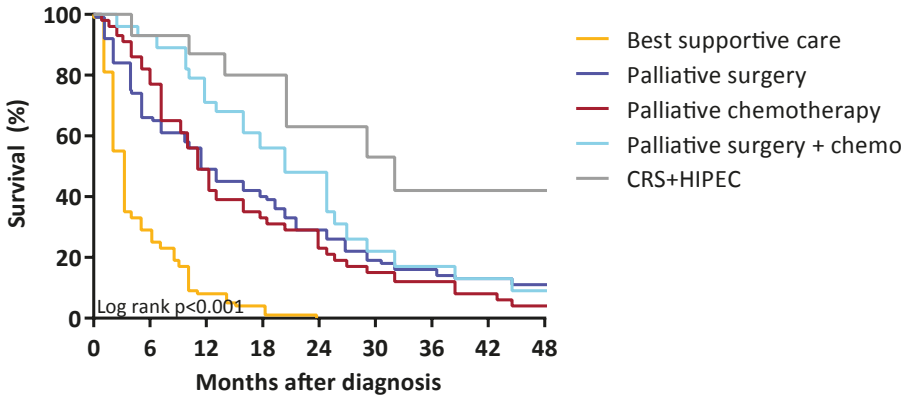
Table 3. Multivariable logistic regression modelling the risk of PM among all patients with SBA diagnosed between 2005 and 2014 in the Netherlands (n = 1428).

	Odds ratio (OR)	95% CI
Sex		
Male	1.0	(reference)
Female	1.2	(0.8-1.6)
Age (years)		
< 70	1.0	(reference)
≥ 70	0.6	(0.5-0.9)
Location of primary tumour		
Duodenum	1.0	(reference)
Jejunum	2.5	(1.6-3.9)
Ileum	3.2	(2.0-5.1)
NOS	2.6	(1.5-4.6)
T-stage		
T1-3	1.0	(reference)
T4	2.1	(1.4-3.2)
Tx	2.0	(1.2-3.4)
N-stage		
N0	1.0	(reference)
N+	1.8	(1.2-2.7)
Nx	3.8	(2.4-6.2)
Period		
2005-2009	1.0	(reference)
2010-2014	2.0	(1.4-2.8)

NOS = not otherwise specified; CI = confidence interval; SBA = small bowel adenocarcinoma.

The median overall survival for all patients with PM was 5.9 months, with a 1-year survival rate of 25%. With supportive care only, median overall survival was 2.5 months. Median overall survival increased to 11 months in patients who were treated with palliative chemotherapy, also to 11 months after surgery of the primary tumour, to 20 months after combined tumour resection and palliative chemotherapy and to 32 months after CRS+HIPEC (figure 2). Over time, survival rates remained stable and did not improve. Survival rates differed between the primary tumour locations. Patients with a primary duodenal tumour had a median overall survival of 3.0 months (1-year survival rate 15%), compared to 8.6 months (1-year survival rate 34%) in patients with a primary non-duodenal tumour ($p < 0.0001$).

Figure 2. Median overall survival of patients with PM of SBA in the Netherlands between 2005 and 2014 per treatment regimen.



	Time to event (months)								
Patients at risk (n)	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**
Best supportive care	75	20	5	2	0	0	0	0	0
Palliative surgery	43	20	11	11	6	4	3	2	2
Palliative chemotherapy	29	18	5	3	2	2	1	1	0
Palliative surgery + chemotherapy	19	17	12	8	6	3	3	2	1
CRS+HIPEC	15	14	13	10	6	5	4	4	4

Chemo = chemotherapy; CRS+HIPEC = cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PM = peritoneal metastases; SBA = small bowel adenocarcinoma.

Univariable and multivariable proportional hazards regression analyses modelling the risk of death for patients with PM of SBA are shown in table 4. In univariable survival analysis of patients with PM, almost all patient, tumour and treatment characteristics seemed to

be of prognostic significance. In multivariable survival analysis, age ≥70 years, an advanced or unknown T-stage and other metastases besides PM were associated with lower survival, whereas surgery of the primary tumour, palliative chemotherapy and CRS+HIPEC were associated with higher survival.

Table 4. Crude median overall survival, univariable and multivariable proportional hazards regression analysis modelling risk of death for patients with PM of SBA in the Netherlands between 2005 and 2014 (n = 181).

	Crude median overall survival (months)	Univariate log rank analysis, *p*-value	Multivariate HR	(95% CI)
Sex		0.09		
Male	4.8		1.0	(reference)
Female	6.9		0.8	(0.6-1.1)
Age (years)		< 0.01		
< 70	7.2		1.0	(reference)
≥ 70	4.6		1.6	(1.1-2.2)
Location of primary tumour		< 0.001		
Duodenum	3.0		1.0	(reference)
Jejunum	11.1		0.7	(0.4-1.2)
Ileum	5.1		1.3	(0.8-2.1)
NOS	9.5		0.8	(0.5-1.5)
T-stage		< 0.0001		
T1-3	11.8		1.0	(reference)
T4	5.9		1.9	(1.3-3.0)
Tx	3.0		2.1	(1.2-3.5)
N-stage		0.03		
N0	5.6		1.0	(reference)
N+	7.4		0.8	(0.5-1.1)
Nx	4.7		0.9	(0.6-1.4)
Metastases		0.03		
PM only	7.2		1.0	(reference)
PM + other	3.1		2.0	(1.4-2.9)
Period		0.98		
2005-2009	5.9			
2010-2014	5.8			
Primary tumour surgery		< 0.0001		
Yes	11.4		0.5	(0.3-0.9)
No	3.1		1.0	(reference)
Palliative chemotherapy		< 0.0001		
Yes	11.1		0.6	(0.4-0.8)
No	3.0		1.0	(reference)
CRS+HIPEC		< 0.0001		
Yes	32.0		0.3	(0.1-0.7)
No	5.0		1.0	(reference)

NOS = not otherwise specified; PM = peritoneal metastases; CRS+HIPEC = cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; HR = hazard ratio; CI = confidence interval; SBA = small bowel adenocarcinoma.

Discussion

This is the first population-based study reporting on the incidence, risk factors and overall survival of patients with synchronous PM from SBA. Our study revealed that 1 in 8 Dutch patients with SBA presented with synchronous PM. PM was most likely to occur in the small bowel distal to the duodenum (17%). Furthermore, the risk of being diagnosed with synchronous PM was higher in patients with an advanced or unknown T- and N-stage and diagnosis in the period 2010-2014. Although median overall survival was poor, higher survival rates were achieved in the selected group of treated patients.

Almost half of all synchronous PM of SBA originated from duodenal tumours. As the duodenal site accounts for approximately 60% of all tumours in primary SBA, the absolute number of synchronous PM of duodenal origin is higher than mentioned in some previous studies[1, 2, 5]. Synchronous PM according to primary tumour location was found in 9% of the patients with a primary duodenal tumour, compared to 17% of the patients with a more distal tumour. This difference might be explained by the earlier symptoms in patients with primary duodenal tumours and by the retroperitoneal location of the duodenum, which makes direct contiguous tumour spread less likely than for tumours in intraperitoneally located organs, such as the jejunum and the ileum[8, 15].

Patients with PM of SBA were slightly younger and predominantly female. Also, in this group, an advanced or unknown T- and N-stage was more common than in the overall group of SBA patients. These findings are in line with the differences between patient and tumour characteristics of patients with PM of CRC and those of all CRC patients. Risk factors for PM of SBA and PM of CRC, as identified in multivariable logistic regression, match to a great extent[9]. However, the percentage of patients presenting with synchronous PM of SBA (13%) was almost three times higher than the incidence of PM in patients with CRC (4-5%)[9, 16, 17].

Surgery with primary tumour resection was performed almost seven times more often in patients with PM of non-duodenal origin than in patients with a primary duodenal tumour. The explanation for this difference is that in case of duodenal tumours, the patient burden of major and complex surgery with substantial risk of mortality and postoperative complications is not proportional to the potential benefits, considering the palliative nature of these interventions[1, 18].

The proportion of patients with PM of SBA who received palliative chemotherapy is in line with previous studies reporting on the usage of palliative chemotherapy in patients with metastatic SBA[1, 2, 5, 19, 20]. Of note, we found that systemic therapy was administered twice as frequently in patients with PM of a primary jejunal or ileal tumour than in patients with PM

of duodenal origin.

In the present study, palliative chemotherapy resulted in a median overall survival of 11 months, which is broadly equivalent to the results of earlier retrospective observational studies[1, 20-23]. Since it is thought that SBA and CRC are similar in terms of carcinogenesis and, to some extent, in terms of tumour behaviour, treatment regimens for SBA, especially chemotherapeutical treatment, are extrapolated from CRC[24, 25]. Various studies have already demonstrated that the most beneficial effect on survival in metastatic SBA seems to be achieved with combination chemotherapy regimens as used in CRC, consisting of fluorouracil and platinum compounds[20, 23, 25-27].

The highest survival was observed in patients who received CRS+HIPEC. However, it should be mentioned that only a small group of highly selected patients with probably limited peritoneal tumour spread and a good general condition, as partly reflected in these patients' younger age, have undergone CRS+HIPEC. We found survival rates of more than 30 months, which were also achieved after CRS+HIPEC in patients with PM of CRC, where CRS+HIPEC is regarded as the standard of care for selected patients[28]. Indeed, other small series reported that CRS+HIPEC seemed to contribute significantly to prolonged survival in a substantial number of patients with PM of SBA[3, 6, 7, 29, 30]. Despite these promising results, it was remarkable that almost half of all CRS+HIPEC procedures were performed in the same centre, while there are eight tertiary referral centres for CRS+HIPEC in the Netherlands, suggesting that not all centres offer all their suitable patients CRS+HIPEC, probably because the potential beneficial effect of CRS+HIPEC on survival has not been proven by a randomised controlled trial (RCT) in patients with PM of SBA. However, all these results together seem to suggest that CRS+HIPEC could be a reasonable treatment option for selected patients with PM of SBA[3, 8, 29].

Of course, due to the population-based nature of our study, these results should be interpreted with caution. Unfortunately, the database of the NCR does not provide detailed information on performance status, the extent of peritoneal burden of the disease, the regimen of the systemic therapy or other prognostic factors. Ideally, an RCT should be performed to demonstrate the value of the various available therapies. However, it is difficult to conduct large and successful prospective clinical studies, given the rarity of small bowel cancer, as also demonstrated by the RARECARE group, which showed the incidence of small bowel cancer to be the lowest among all rare epithelial digestive cancers[31]. Meanwhile, the present study might provide helpful insight into PM of SBA, as it showed that certain subgroups of selected patients might benefit from treatment. Nevertheless, it should be reiterated that this is an observational study, and therefore, no statements can be made

about the precise effect of a therapy, because patients for all treatment arms were highly selected by their clinicians.

In conclusion, although SBA is a rare disease, synchronous PM was frequently encountered, affecting more than 1 in 6 patients with a primary non-duodenal tumour and approximately 1 in 10 patients with a primary duodenal adenocarcinoma. This study observed a significant higher median overall survival for the selected group of treated patients. Analogous to PM of CRC, it could be that a multidisciplinary approach might result in a better patient selection for specific patient tailored treatment options including aggressive therapy such as CRS+HIPEC.

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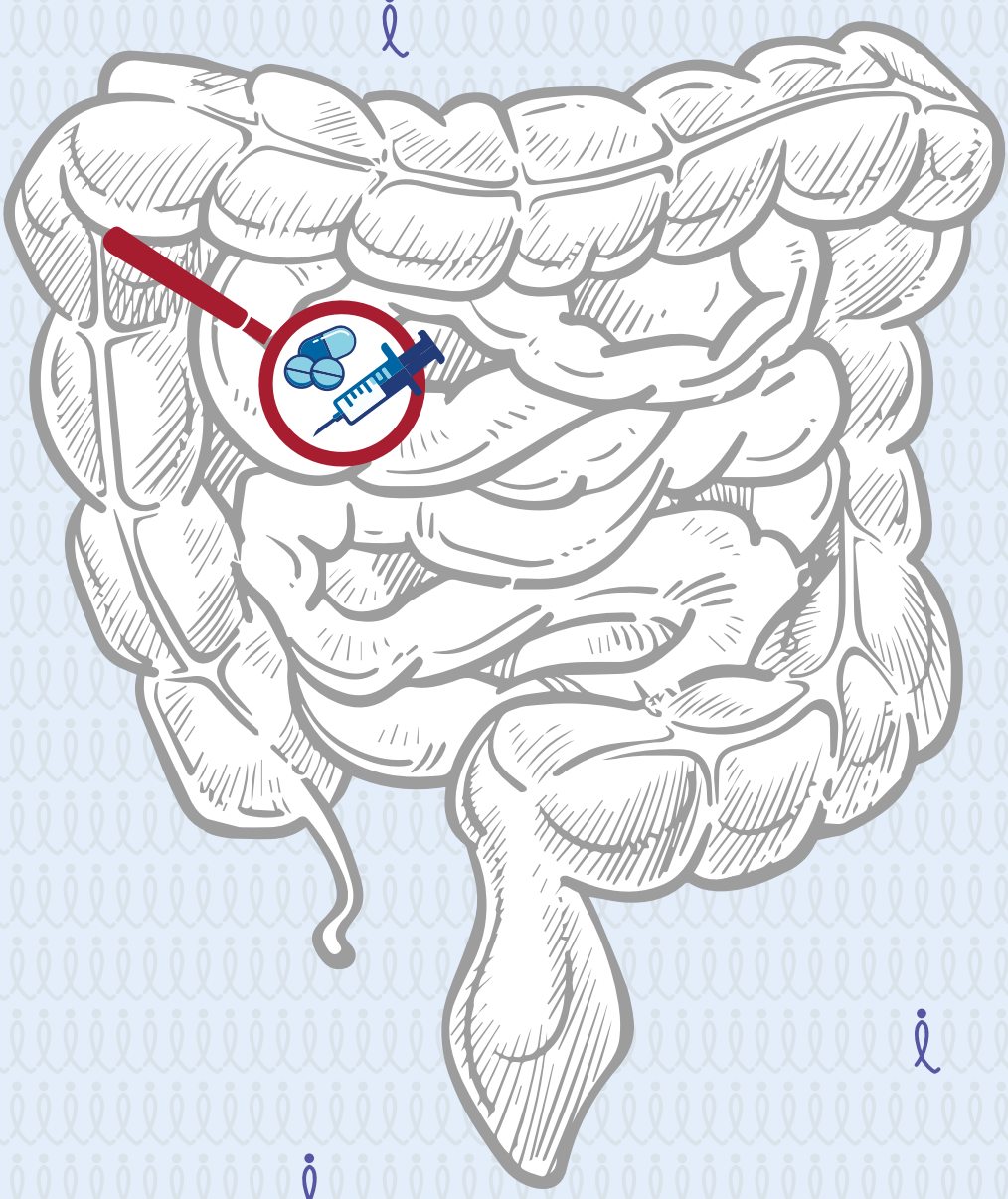
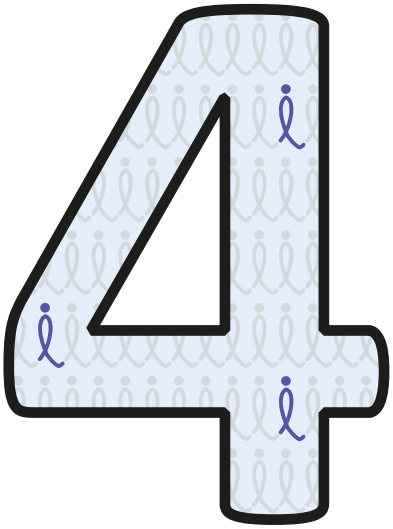
Part II

Palliative systemic therapy in metastatic small bowel cancer





Palliative chemotherapy for patients with synchronous metastases of small bowel adenocarcinoma:

A reflection of daily practice

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Abstract

Background: As small bowel adenocarcinoma (SBA) is scarce, no standard systemic regimen in metastatic disease has been defined.

Objective: To obtain insights into the use and effects of palliative chemotherapy in patients with metastatic SBA in a population-based setting.

Methods: Data from the Netherlands Cancer Registry of patients with metastatic SBA between 2007 and 2016 were used (n = 522). For patients treated with palliative chemotherapy, differences in treatment regimens and survival were evaluated.

Results: Palliative chemotherapy was received by 38% of the patients (n = 199). First-line combination chemotherapy was administered to 80% of the patients, mainly CAPOX/FOLFOX. Single-agent chemotherapy mostly consisted of capecitabine. Second-line treatment was prescribed to 27% of the patients, mostly irinotecan-based (58%). Age 70 years of older was an adverse predictive factor for receiving first-line combination chemotherapy (OR 0.2, 95%CI 0.08-0.62) and second-line therapy (OR 0.3, 95%CI 0.10-0.72). Median overall survival with palliative chemotherapy was 9.3 months, compared with 3.0 months without. In sub analyses, patients who only received first-line treatment had a median overall survival of 5.6 and 7.0 months after single-agent and combination chemotherapy, respectively.

Conclusion: A minority of patients were treated with palliative chemotherapy. First-line treatment consisted predominantly of oxaliplatin-based combination chemotherapy, whereas second-line treatment was mainly irinotecan-based. Population-based median overall survival for selected patients treated with chemotherapy amounted to 9 months.

Introduction

Small bowel adenocarcinoma (SBA) is a rare gastro-intestinal tumour, accounting for only 2-3% of all malignant digestive tumours. In SBA patients, metastatic disease is a common phenomenon, as approximately 30 to 40% of patients presents with synchronous metastases[1-4]. It has been hypothesised that these high metastatic rates are caused by the nonspecific and atypical symptoms in patients and the lack of simple and reliable diagnostic tools to reach the small bowel. The prognosis of patients with metastatic SBA is poor with a reported overall survival of 4-11 months[2, 3].

Due to the rarity of the disease, most data on palliative chemotherapy in SBA are derived from phase II trials and retrospective series of mainly high-volume or tertiary medical centres[5-7]. These studies have demonstrated that chemotherapy prolongs overall survival in patients with metastatic SBA[4-15]. However, in the absence of randomised controlled trials, a standard chemotherapeutical regimen has not been defined. Patients are usually treated with chemotherapeutical regimens which have been extrapolated from other gastrointestinal cancers. Several studies have demonstrated that combination chemotherapy consisting of a fluoropyrimidine and platinum compound seems to have the most beneficial effect on survival, with median overall survival rates ranging between 14 and 18 months[4, 7, 12, 14, 15]. As a result, a frontline regimen of platinum-based combination chemotherapy has been suggested[7, 16].

Population-based data, which reflect daily practice and could be of help for clinicians to guide treatment decisions, are currently lacking. As large prospective clinical studies and randomised controlled trials are virtually impossible to conduct due to the rarity of SBA, this population-based study was performed to provide insight into the daily-based chemotherapeutical treatment and its results in patients with synchronous metastatic SBA.

Material and Methods

Data collection

Data were obtained from the population-based Netherlands Cancer Registry (NCR). The nationwide NCR covers all nearly 17 million inhabitants of the Netherlands and collects data on all newly diagnosed malignancies. Primary source of notification is the automated nationwide pathological archive (PALGA), accompanied with data from the National Registry of Hospital Discharge Diagnoses. Information on patient and tumour characteristics, diagnosis and treatment were routinely collected from medical records by specially trained administrators. In the NCR, the primary tumour stage was determined based on the tumour-node-metastasis (TNM) classification. In case the pathological TNM stage was missing, the clinical TNM stage was used. The anatomical site of the primary tumour and its metastases were recorded according to the third version of the International Classification of Disease for Oncology (ICD-O).

For the present study, additional data were retrospectively collected by registry clerks of the NCR on systemic treatment regimens for patients treated with palliative chemotherapy for synchronous metastases of small bowel adenocarcinoma (ICD-O code C17) diagnosed between 2007 and 2016. Synchronous metastases were defined as metastases diagnosed within 3 months after the initial SBA diagnosis. The additional data comprised information on first-, second- and third-line systemic treatment regimens, including details and duration of the chemotherapeutical and targeted agents. First-line systemic treatment was defined as the initial therapy with chemotherapeutical and/or targeted agents. If one of the agents of the initial therapy was discontinued, while other drug(s) were continued, it was still regarded as first-line treatment. Second- and third-line systemic treatment was defined as the adoption of a different treatment regimen, mostly because of failure of first-line therapy or unacceptable toxicities. In case of a rechallenge of a chemotherapeutical and/or targeted agent within 3 months or after maintenance therapy, we defined the therapy to be a next line treatment. If the rechallenge occurred after 3 months, without maintenance therapy, the therapy was classified as the same-line treatment.

Statistical analysis

Descriptive statistics were used to describe the patient and tumour characteristics of the study population. Differences in patient- and tumour characteristics between the treated and nontreated patients were analysed with a two-sided chi-square test. In all analyses concerning palliative chemotherapy, only the patients receiving palliative chemotherapy with a known treatment regimen were included. First-, second- and third-line systemic treatment regimens were categorised according to the administrated number of chemotherapeutical agents into single-agent chemotherapy and combination chemotherapy, apart from the

additional administration of targeted agents. Time to progression from the start of first- to start of second-line treatment and second- to third-line treatment was calculated and presented in months. Differences in time to progression from first- to second-line treatment between the patients receiving single-agent chemotherapy and combination chemotherapy was evaluated with the Wilcoxon rank-rum test. Univariable logistic regression, including the 95% confidence interval (CI), was used to assess the independent influence of all patients and clinical characteristics on the probability of receiving second-line treatment. If univariable analyses tended towards statistical significance ($p < 0.20$), the probability of receiving second-line treatment corrected for these potential prognostic factors was afterwards calculated with multivariable regression analyses. For the odds of receiving first-line combination chemotherapy, only multivariable logistic regression analyses were run.

Overall survival was calculated on mortality of any cause. Overall survival time was defined as the time from date of diagnosis to death or last follow-up date. Patients who were lost to follow-up, emigrated or still alive at 1 February 2018 were censored. Overall survival was estimated with the log-rank test and Kaplan-Meier analyses. Median overall survival was presented in months, with its corresponding 95% CIs. The median overall survival of the treated patients was compared to the patients only receiving best supportive care. Multivariable cox proportional hazards regression analyses were performed to identify prognostic factors for overall survival in patients treated with palliative chemotherapy. Hazard ratios (HRs) were presented with its corresponding 95% CIs.

The statistical package SAS Statistical Software (version 9.4, SAS Institute, Cary, NC, USA) was used to analyse the data. A two-sided p-value of $p < 0.05$ was considered as statistically significant for all statistical tests.

Results

Patients

A total of 522 patients were diagnosed with synchronous metastases of small bowel adenocarcinoma between 2007 and 2016, of whom 199 patients (38%) received palliative systemic treatment. Multiple patient- and tumour characteristics differed between the treated patients and the nontreated patients, as shown in table 1. Patients treated with chemotherapy were significantly younger, with a median age of 63 years, compared with 72 years in non-treated patients ($p < 0.0001$). A nonsignificant trend was observed with respect to the primary tumour site, as relatively more patients with a distal tumour received systemic treatment than patients with a primary duodenal tumour ($p = 0.10$). Patients with a higher metastatic tumour load were treated more frequently than patients with solitary metastases ($p < 0.001$), which was not affected by the potential influence of surgical resection of metastatic sites among the different subgroups ($p = 0.53$). Over time, the percentage of treated with chemotherapy remained stable at 35 to 40%. Among treated patients, the exact treatment regimen was known in 187 patients (94%). Only these patients were included for all further analyses concerning palliative chemotherapy.

In patients receiving palliative chemotherapy, the primary tumour was mainly located in the duodenum (60%), followed by the jejunum (20%) and ileum (12%). Patients presented with liver and peritoneal metastases in 63% and 36% of the cases, respectively. In 40% of the patients multiple metastatic sites were diagnosed. Only 2 patients were diagnosed with Lynch syndrome. In 66 patients (35%) palliative interventions were performed, including surgical bypass and stenting, mostly in patients with a primary duodenal tumour (79%).

Chemotherapy regimens

The first-line chemotherapy regimens were mainly based on fluoropyrimidines (5-fluorouracil and capecitabine) and oxaliplatin (figure 1). Combination chemotherapy was prescribed to 80% of the patients, of whom 97% received an oxaliplatin-based doublet or triplet regimen, including capecitabine (CAPOX, n = 91), 5-fluorouracil (FOLFOX, n = 29) or epirubicin with capecitabine (EOX, n = 2). Single-agent chemotherapy was administered to 20% of the patients, consisting of fluoropyrimidines in 92% of the cases, mainly capecitabine (n = 32). The targeted agent bevacizumab was prescribed to 13% of the patients (n = 25), most frequently in addition to combination chemotherapy. Other nonfrequently used first-line treatment regimens included epirubicin, cisplatin and capecitabine (ECC, n = 2), carboplatin with paclitaxel (n = 2), capecitabine with irinotecan (CAPIRI, n = 1) and oxaliplatin (n = 2) or irinotecan monotherapy (n = 1).

Table 1. General characteristics of the total patient population according to palliative chemotherapy treatment (n = 522) and of patients treated with palliative chemotherapy according to first-line chemotherapy regimen (n = 187).

	Palliative chemotherapy					First-line treatment				
	Yes (n = 199)		No (n = 323)			Single-agent chemotherapy (n = 37)		Combination chemotherapy (n = 150)		
	N	(%)	N	(%)	*p*-value	N	(%)	N	(%)	*p*-value
Gender					0.86					0.55
Male	102	(51.3)	163	(50.5)		21	(56.8)	77	(51.3)	
Female	97	(48.7)	160	(49.5)		16	(43.2)	73	(48.7)	
Age (years)					< 0.0001					< 0.01
<60	71	(35.7)	54	(16.7)		9	(24.3)	59	(39.3)	
60-69	71	(35.7)	89	(27.5)		10	(27.0)	57	(38.0)	
≥70	57	(28.6)	180	(55.7)		18	(48.7)	34	(22.7)	
Period					0.21					< 0.001
2007-2010	64	(32.2)	113	(35.0)		21	(56.8)	37	(24.7)	
2011-2013	64	(32.2)	115	(35.6)		10	(27.0)	53	(35.3)	
2014-2016	71	(42.8)	95	(29.4)		6	(16.2)	60	(40.0)	
Location primary tumour					0.10					0.86
Duodenum	119	(59.8)	226	(70.0)		24	(64.9)	88	(58.7)	
Jejunum	39	(19.6)	42	(13.0)		7	(18.9)	31	(20.7)	
Ileum	24	(12.1)	32	(9.9)		3	(8.1)	20	(13.3)	
NOS	17	(8.5)	23	(7.1)		3	(8.1)	11	(7.3)	
Number of affected metastatic sites					< 0.001					0.12
1	122	(61.3)	241	(74.6)		21	(56.8)	91	(60.7)	
2	46	(23.1)	61	(18.9)		13	(35.1)	32	(21.3)	
≥ 3	31	(15.6)	21	(6.5)		3	(8.1)	27	(18.0)	

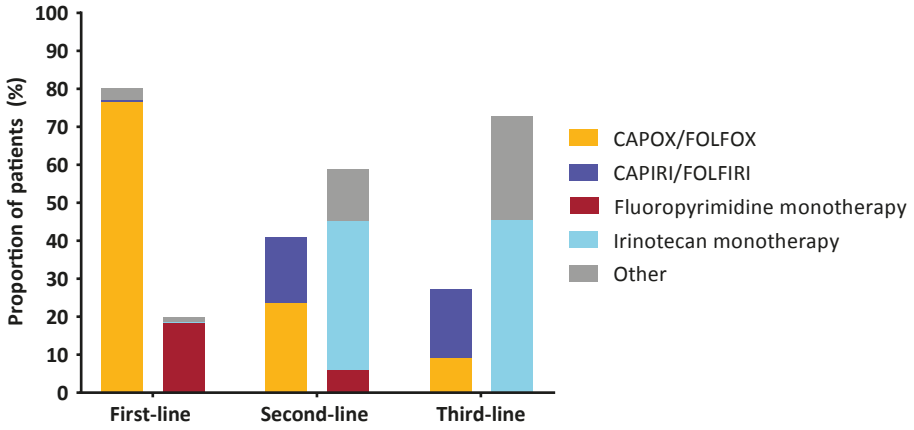
NOS = not otherwise specified.

Logistic regression showed significant differences between the prescription of single-agent chemotherapy and combination chemotherapy in first-line treatment (table 2). Combination chemotherapy was less frequently administered to elderly patients (≥70 years) and in the first time period (2007-2010).

Second-line systemic therapy was received by only 27% of the patients (n = 50), mostly consisting of single-agent chemotherapy (58%) (figure 1). Irinotecan was administered as a single-agent in 69% of the patients (n = 20). Patients treated with combination chemotherapy, received an oxaliplatin-based (n = 12) or an irinotecan-based (n = 9) regimen with either capecitabine (CAPOX/CAPIRI) or 5-fluorouracil (FOLFOX/FOLFIRI). In 7 patients who received a second-line oxaliplatin-based regimen, a rechallenge after use of oxaliplatin-based combination chemotherapy in first-line occurred. Epidermal growth factor receptor

(EGFR) monotherapy was administered to 2 patients. In 8 patients, bevacizumab was prescribed in addition to second-line chemotherapy.

Figure 1. The prescribed chemotherapeutic regimens according to combination chemotherapy and single-agent chemotherapy in first-, second- and third-line treatment in metastatic small bowel adenocarcinoma.



Logistic regression analysis identified advanced age (≥70 years) to be inversely associated with the receipt of second-line treatment (OR 0.26, 95% CI 0.10-0.72) (table 2).

Third-line systemic therapy was received by 11 patients (6%). Most third-line regimens were irinotecan-based (n = 8), consisting of irinotecan monotherapy (n = 3), or combination therapy of a fluoropyrimidine with irinotecan (CAPIRI/FOLFIRI, n = 3) (figure 1). The targeted agent panitumumab was used in 4 patients (36%), either as monotherapy (n = 2) or in combination with irinotecan (n = 2).

Survival

The median overall survival for patients treated with palliative chemotherapy and a known systemic treatment regimen was 9.3 months, with a 1-year survival rate of 39%. Patients only receiving best supportive care had a median overall survival of 3.0 months, with a 1-year survival rate of 17%. In patients only receiving first-line treatment, the median overall survival of patients receiving single-agent chemotherapy was 5.6 months, compared with 7.0 months with combination chemotherapy, with 1-year survival rates of 22% and 29%, respectively. The median time to progression from first- to second-line therapy was 7.7 months, which did not significantly differ between the single-agent chemotherapy and combination chemotherapy group (p = 0.82).

Table 2. General characteristics and multivariable logistic regression modelling the odds of patients receiving combination therapy in first-line treatment (left) and general characteristics, univariable logistic regression and multivariable logistic regression modelling the odds of receiving second-line treatment compared to patients receiving first-line treatment (right).

(n = 187)	Combination chemotherapy in first-line		Multivariable logistic regression		Second-line treatment		Univariable logistic regression	Multivariable logistic regression	
	N	(%)	OR	(95% CI)	N	(%)	*p*-value	OR	(95% CI)
Gender							0.21		
Male	77	(78.6)	1.00	reference	30	(30.6)			
Female	73	(82.0)	1.28	(0.57-2.88)	20	(22.5)			
Age (years)							0.01		
<60	59	(86.8)	1.00	reference	25	(36.8)		1.00	reference
60-69	57	(85.0)	0.87	(0.31-2.49)	19	(28.4)		0.77	(0.36-1.62)
≥70	34	(65.4)	0.22	(0.08-0.62)	6	(11.5)		0.26	(0.10-0.72)
Period							0.15		
2007-2010	37	(63.8)	1.00	reference	18	(31.0)		1.00	reference
2011-2013	53	(84.1)	2.72	(1.08-6.86)	20	(31.7)		0.94	(0.42-2.11)
2014-2016	60	(90.9)	7.28	(2.47-21.45)	12	(18.2)		0.49	(0.20-1.17)
Location primary tumour							0.69		
Duodenum	88	(78.6)	1.00	reference	28	(25.0)			
Jejunum	31	(81.6)	1.31	(0.44-3.89)	13	(34.2)			
Ileum	20	(87.0)	2.17	(0.55-8.58)	6	(26.1)			
NOS	11	(78.6)	1.00	(0.21-4.77)	3	(21.4)			
Number of affected metastatic sites							0.10		
1	91	(81.3)	1.00	reference	25	(22.3)		1.00	reference
2	32	(71.1)	0.47	(0.18-1.20)	14	(31.1)		1.57	(0.70-3.52)
≥ 3	27	(90.0)	1.49	(0.36-6.17)	12	(40.0)		2.25	(0.91-5.57)
First-line chemotherapy							0.96		
Single-agent					10	(27.0)			
Combination					40	(26.7)			

NOS = not otherwise specified, OR = Odds ratio, CI = confidence interval

Patients receiving second-line systemic therapy had a significant higher median overall survival, compared with those who only received first-line therapy, with observed median overall survival times of 15.2 and 6.8 months respectively ($p < 0.0001$). In the 11 patients receiving third-line treatment, a median overall survival of 28.4 months was noted. Among this subgroup of patients, 5 out of 11 had a rechallenge of CAPOX/FOLFOX (n = 4) or capecitabine monotherapy (n = 1) in second-line treatment. The median time to progression from second- to third-line systemic therapy was 9.8 months.

Multivariable survival analyses showed, after adjustment for different patient- and clinical characteristics, including use of second-line and third-line therapy, that patients with jejunal tumours (HR 0.51, 95% CI 0.33-0.79) and those who received second-line systemic therapy (HR 0.42, 95% 0.29-0.63) had a higher overall survival (table 3).

Table 3. Multivariable survival analyses for patients treated with palliative chemotherapy in synchronous metastatic small bowel adenocarcinoma (n = 187).

	Crude median overall survival (months)	**HR**	**(95% CI)**
Gender			
Male	9.3	1.00	(reference)
Female	9.3	0.88	(0.63-1.21)
Age (years)			
<60	8.6	1.00	(reference)
60-69	10.7	1.03	(0.70-1.51)
≥70	8.3	0.87	(0.57-1.33)
Period			
2007-2010	10.5	1.00	(reference)
2011-2013	10.7	1.00	(0.68-1.46)
2014-2016	6.5	1.06	(0.72-1.57)
Location primary tumour			
Duodenum	8.2	1.00	(reference)
Jejunum	13.2	0.51	(0.33-0.78)
Ileum	11.5	0.65	(0.40-1.05)
NOS	5.8	1.41	(0.78-2.57)
Number of affected metastatic sites			
1	8.8	1.00	(reference)
2	10.0	0.98	(0.67-1.45)
≥ 3	7.8	1.31	(0.82-2.10)
Lines of chemotherapy			
First-line	6.8	1.00	(reference)
Second-line	15.2	0.42	(0.29-0.63)
Third-line	28.4	0.67	(0.33-1.36)

NOS = not otherwise specified, HR = hazard ratio, CI = confidence interval

Discussion

This population-based study aimed to provide insight into the community-based use of palliative chemotherapy in patients with synchronous metastases of SBA. Palliative chemotherapy was administered to 38% of the patients with metastatic disease. The vast majority of treated patients received an oxaliplatin-based combination regimen in first-line treatment with CAPOX/FOLFOX. Second-line therapy was administered to only 27% of the patients, with mainly irinotecan monotherapy.

In first-line treatment, combination chemotherapy with mainly an oxaliplatin-containing regimen was most often prescribed, analogous to gastric cancer and colorectal cancer (CRC), for which fluoropyrimidines and platinum derivatives are the backbone of palliative chemotherapy[17, 18]. In the present study, only a small minority of patients with a primary duodenal tumour were classically treated as gastric cancer with triplet chemotherapy as ECC or EOX, probably as it was historically thought that duodenal tumours more behave like gastric cancer, whereas distal tumours share more similarities with CRC[6]. In recent years, several studies conducted on the efficacy of chemotherapy in advanced gastric cancer have favoured the use of oxaliplatin over cisplatin in terms of its toxicity profile and its noninferiority in overall survival, and have questioned a beneficial effect on survival from the contribution of anthracyclines as epirubin to an oxaliplatin-based combination regimen[18-20]. As a result, both CAPOX/FOLFOX are a well-studied and effective first-line palliative treatment regimen in a variety of gastro-intestinal cancers, including gastric cancer and CRC. These obtained results suggested a potential role for this regimen in metastatic SBA, because of the embryological derivation of the small bowel and the presence of some overlapping genomic alterations both with gastric cancer and CRC[21]. Other small retrospective and phase II studies conducted on the efficacy of CAPOX/FOLFOX in metastatic SBA showed improved survival rates in treated patients with tolerable toxicity[4, 7, 12, 14, 15].

Combination chemotherapy in first-line treatment was increasingly administered over time, although all used cytotoxic agents were registered and available during the total study period in the Netherlands[22-24]. Hypothetically, the obtained experience of clinicians with these cytotoxic drugs in more frequently encountered gastrointestinal cancers, and the obtained evidence of the beneficial effect of oxaliplatin-based regimens in phase II studies for metastatic SBA, could account for the increased use of combination chemotherapy over time[5, 7, 14].

Second-line therapy was administered to only about a quarter of the patients, which is limited, even on a population-based level, as compared with patients receiving second-line treatment in metastatic disease of gastric cancer and CRC[25-27]. Possibly, the lack of data for second-line chemotherapy in SBA could be accountable for these lower rates.

Second-line treatment was mainly irinotecan-based, and 40% of the patients received irinotecan monotherapy, which could have been influenced by the favourable results of second-line FOLFIRI in establishing disease control after failure of first-line platinum-based chemotherapy as reported in a French study[28]. The prescription of irinotecan-based second-line chemotherapy is in accordance to the Dutch guidelines for second-line treatment for metastatic CRC, but not for gastric cancer[29]. Of note, the median time to progression between first- and second-line treatment is comparable for SBA and CRC[30-32].

The median overall survival of 6 to 9 months as found in the current study is lower than survival rates that are reported in other retrospective studies, although equivalent treatment regimens were used[4, 11, 12]. In the present study, the median age was slightly higher and more patients had liver metastases compared with other retrospective studies. Moreover, no patients with locally advanced disease were included in the current study, whereas one study did include patients both with locally advanced and metastatic disease of SBA[4]. In comparison to patients in population-based studies treated with palliative chemotherapy for other gastro-intestinal cancers, patients with metastatic SBA have a worse median overall survival than patients with metastatic CRC, whereas the survival of patients with metastatic SBA and gastric cancer is comparable[33, 34].

Patients who received first-line chemotherapy only had a higher overall survival of 3 to 4 months compared with patients receiving best supportive care. However, selection bias should be taken into account as patients treated with palliative chemotherapy were already selected by their treating physician, as for instance reflected in a lower median age. On a population-based level, a doubling of median overall survival was observed in patients receiving first-line combination chemotherapy.

The highly selected group of patients who were prescribed second-line or even third-line treatment had a median overall survival of almost 15 and 28 months, respectively. However, immortal time bias could have influenced these results and should be taken into account, since patients should be alive to receive further line chemotherapy. Moreover, considering nearly half of the patients treated with third-line therapy had a rechallenge of oxaliplatin doublet chemotherapy or capecitabine monotherapy in second-line treatment, it could suggest that these patients had a more indolent tumour behaviour or their tumours had a prolonged or increased chemosensitivity to oxaliplatin-containing combination chemotherapy. The impact of irinotecan on median overall survival in second- and third-line treatment needs to be studied in a larger subset of patients.

As already stated, selection bias is a potential drawback of the current study with regards

to overall survival. Furthermore, detailed information on for instance performance status, nutritional status, comorbidities, disease-related symptoms and the extent of disease were lacking, since these data were not provided in the databases of the NCR or were often not noted in the patient records.

In conclusion, a minority of patients with synchronous metastases of SBA were treated with palliative chemotherapy in daily practice. First-line treatment consisted predominantly of oxaliplatin-based combination chemotherapy, whereas second-line treatment was mainly irinotecan-based. Population-based median overall survival for selected patients treated with chemotherapy amounted to 9 months.

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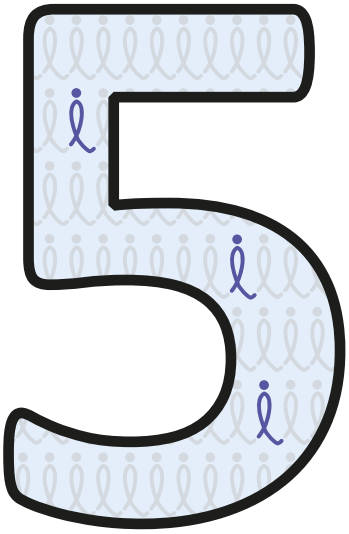

Addition of bevacizumab to first-line palliative chemotherapy in patients with metastatic small bowel adenocarcinoma:

A population-based study

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Abstract

Background: Data about the use and effectiveness of targeted therapy in metastatic small bowel adenocarcinoma (SBA) are scarce. The aim of this population-based study was to obtain insights into the use and effectiveness of targeted therapy in patients with synchronous metastases of SBA.

Material and methods: Data were retrieved from the Netherlands Cancer Registry. Patients treated with palliative chemotherapy and/or targeted therapy for synchronous metastatic SBA between 2007 and 2016 were included (n = 187). Differences in treatment with and without targeted therapy and the subsequent effects on overall survival (OS) were evaluated.

Results: In first-line treatment, 25 patients (13%) received additional targeted therapy, exclusively bevacizumab, and mostly in combination with CAPOX/FOLFOX (n = 24). A primary ileal tumour was the only positive predictive factor for receiving bevacizumab in first-line treatment (OR 3.2, 95% CI 1.06-9.93). Median OS for patients in whom bevacizumab was added to first-line chemotherapy was 9.3 months, compared to 9.1 months with chemotherapy only (p = 0.85). Median OS for patients receiving first-line treatment only, was 8.5 months with and 6.4 months without the addition of bevacizumab respectively (p=0.54). In multivariable survival analyses, the addition of bevacizumab was no prognostic factor (HR 1.01, 95% CI 0.65-1.59).

Conclusion: Bevacizumab was the only prescribed targeted therapy in first-line treatment. Considering the limited numbers of patients receiving first-line bevacizumab and the unkown reasons to prescribe additional targeted therapy, the corresponding survival rates of patients treated with and without additional bevacizumab in first-line treatment, might suggest a limited clinical effect of bevacizumab in addition to first-line palliative chemotherapy on OS. Future research should focus on identifying the subgroup of patients who might benefit from anti-VEGF therapy in metastatic SBA.

Introduction

Small bowel adenocarcinoma (SBA) is rarely encountered, despite the substantial mucosal surface of the small bowel within the gastro-intestinal tract[1]. The duodenum is the most affected primary tumour site in SBA, followed by the jejunum and ileum[2-5]. As early diagnosis is challenging, almost 40% of the patients are diagnosed with synchronous metastatic disease[1, 4, 5]. Overall survival of these patients is poor with a one-year survival rate of approximately 25%[5].

Despite the lack of randomised controlled trials in patients with metastatic SBA, palliative chemotherapy is widely used in daily clinical practice to improve quality of life and prolong survival. The most prescribed chemotherapy regimen in first-line treatment consists of an oxaliplatin-based doublet regimen with fluoropyrimidines[6-10].

In the Netherlands, no guidelines exist for the palliative systemic treatment of metastatic SBA. As SBA and colorectal cancer (CRC) share multiple genomic alterations, treatment regimens for SBA are traditionally extrapolated from CRC[11]. In metastatic CRC, the targeted agents bevacizumab, an anti-VEGF-A (vascular endothelial growth factor-A) monoclonal antibody, and panitumumab and cetuximab, both anti-EGFR (epidermal growth factor receptor) monoclonal antibodies, have demonstrated improvement in progression-free survival (PFS)[12-18]. By analogy, a few reports have recently described the use of targeted agents in SBA[19-24]. Population-based data on the use and effectiveness of targeted therapy in metastatic SBA are currently lacking. Therefore, a population-based study was performed to provide insight into the population-based use and effectiveness of targeted therapy in synchronous metastases of SBA in a nationwide cohort.

Material and Methods

Data collection

Data were retrieved from the Netherlands Cancer Registry (NCR). The NCR covers nearly 17 million inhabitants of the Netherlands and collects population-based data on all newly diagnosed malignancies. The primary source of notification of the NCR is the automated nationwide pathological archive (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses. Specially trained registry clerks of the NCR routinely collect data from medical records, which comprises information on patient and tumour characteristics, diagnosis and treatment. In the databases of the NCR, the primary tumour stage is determined according to the tumour-node-metastasis (TNM) classification. In case of missing pathological data, the clinical TNM stage is used. The anatomical site of the primary tumour and its metastases are registered according to the third version of the International Classification of Disease for Oncology (ICD-O).

For this study, some additional data were retrospectively collected by registry clerks of the NCR on used systemic treatment regimens for patients diagnosed with synchronous metastases of small bowel adenocarcinoma (ICD-O code C17) between 2007 and 2016. Synchronous metastases were defined as metastases diagnosed within 3 months after the initial SBA diagnosis. The additional collected data included detailed information on used first-, second- and third-line systemic treatment regimens of both chemotherapeutical and targeted agents. First-line systemic treatment was defined as the initial started therapy with chemotherapy and/or targeted agents. In case one of the agents of the initial therapy was discontinued, while other(s) continued, it was still regarded as first-line treatment. Second- and third-line systemic treatment was defined as the adoption of a new treatment regimen, mostly due to first-line therapy failure or unacceptable toxicities. In case of a rechallenge of a chemotherapeutical and/or targeted agent within 3 months or after maintenance therapy, the therapy was defined to be a next line treatment. If the rechallenge occurred after 3 months, without maintenance therapy, the therapy was classified as the same line treatment. Patients with unknown systemic treatment regimen were excluded from further analyses.

Vital status of the patients was assessed on 31 January 2019 through linkage of the NCR with civil municipal registries and the central bureau for genealogy, which collects data on all deceased Dutch inhabitants.

Statistical analysis

First, patient and tumour characteristics and treatment modalities were described. Apart from the administration of targeted agents, the use of chemotherapy was taken into account.

First-, second- and third-line systemic treatment regimens were categorized according to the administered number of chemotherapeutical agents into single-agent chemotherapy and combination chemotherapy. Differences in patient and tumour characteristics were analysed with a two-sided chi-squared test or Fisher's exact test in case of small samples. Trends in time were evaluated by means of a Cochran-Armitage trend test. Univariable logistic regression, including the 95% confidence interval (CI), was used to determine the influence of patients and clinical characteristics on the probability of receiving targeted therapy in first-line treatment. As the number of patients were limited, multivariable regression analyses were not performed.

A propensity score matched sample was generated as the use of population-based data could cause potential endogeneity bias when comparing patients with and without additional treatment with bevacizumab in first-line treatment. Propensity scores were determined by means of a logistic regression model in which the administration of bevacizumab in first-line treatment was the variable of interest, and the independent variables were those factors that were significant in univariable logistic regression, in combination with relevant clinical features, including age and type of chemotherapy (single-agent or combination). Patients were matched with tight bounds of the propensity scores, in which the predicted probability could not vary more than 1%.

Overall survival (OS) time was defined as the time from diagnosis to death or date of last follow-up. Patients who were lost to follow-up, emigrated or still alive at 31 January 2019 were censored. Survival was computed on all-cause mortality. The log-rank test and Kaplan-Meier analyses were used to estimate OS. Median OS was presented in months, with its corresponding 95% CIs. Univariable and multivariable cox proportional hazards regression analyses were run to identify prognostic factors for overall survival. Hazard ratios (HRs) were presented with 95% CIs.

Statistical analyses were carried out by the statistical package SAS Statistical Software (version 9.4, SAS Institute, Cary, NC, USA). For all analyses, a two-sided p-value of $p < 0.05$ was considered as statistically significant.

Results

In the period 2007-2016, 522 patients were diagnosed with synchronous metastases of small bowel adenocarcinoma. Palliative systemic treatment was initiated in 199 patients (38%). In 12 patients the treatment regimen was unknown, and these patients were excluded from further analyses.

In the total study population, gender was almost equally distributed and a median age of 63 years was found. Most primary tumours were located in the duodenum (60%). Liver and peritoneal metastases were present in 63% and 36% of the patients respectively. In first-line treatment, combination chemotherapy was administered to 80% of the patients and single-agent chemotherapy to 20% of the patients. Combination chemotherapy mainly consisted of a doublet regimen of CAPOX/FOLFOX (95%). Single-agent chemotherapy consisted largely of capecitabine monotherapy (89%). Of the 187 patients treated with first-line systemic treatment, 25 patients (13%) received targeted therapy, which was exclusively bevacizumab. Patient and tumour characteristics did not significantly differ between the group of patients treated with and without targeted therapy, as shown in table 1. Although not statistically significant, relatively more patients with a primary distal tumour received bevacizumab in addition to first-line treatment than patients with a primary duodenal tumour ($p = 0.13$). Bevacizumab was more often prescribed to combination chemotherapy with CAPOX/FOLFOX ($n = 24$), than to capecitabine monotherapy ($n = 1$) ($p = 0.03$). Over time, there was a slight decrease in prescription of bevacizumab, mainly after 2014 ($p = 0.28$). Moreover, the prescription of bevacizumab was not affected by the hospital of treatment ($p = 0.30$).

Logistic regression analysis modelling the probability to receive bevacizumab in first-line treatment revealed only a primary ileal tumour (OR 3.24, 95% CI 1.06-9.93) as compared to a primary duodenal tumour as a positive predictive factor in univariable analyses (table 2).

In second- or third-line treatment, several targeted agents were prescribed. In the 50 patients receiving second-line systemic therapy, 10 patients (20%) received targeted therapy. Bevacizumab was administered to 8 patients, whereas anti-EGFR monotherapy was prescribed to 2 patients. In the group of patients treated with bevacizumab, it was prescribed in addition to an oxaliplatin-based doublet regimen ($n = 4$), capecitabine monotherapy ($n = 3$) or irinotecan monotherapy ($n = 1$). In 5 of these 8 patients, it was a re-introduction after use of bevacizumab in first-line treatment. In third-line treatment, 4 out of 11 (36%) patients received targeted therapy, solely panitumumab. Panitumumab was prescribed as monotherapy in 2 patients, and in combination with irinotecan in the other 2 patients.

Table 1. General characteristics of patients treated with palliative chemotherapy with and without additional use of bevacizumab in first-line treatment in synchronous metastatic small bowel adenocarcinoma between 2007 and 2016 (n = 187).

	Total		Bevacizumab in first-line treatment				
	(n = 187)		Yes (n = 25)		No (n = 162)		
	N	(%)	N	(%)	N	(%)	*p*-value
Gender							0.70
Male	98	(52.4)	14	(56.0)	84	(51.9)	
Female	89	(47.6)	11	(44.0)	78	(48.2)	
Age (years)							0.68
<60	68	(36.4)	10	(40.0)	58	(35.8)	
60-69	67	(35.8)	7	(28.0)	60	(37.0)	
≥70	52	(27.8)	8	(32.0)	44	(27.2)	
Period							0.28
2007-2010	58	(31.0)	9	(36.0)	49	(30.3)	
2011-2013	63	(33.7)	10	(40.0)	53	(32.7)	
2014-2016	66	(35.3)	6	(24.0)	60	(37.0)	
Location primary tumour							0.13
Duodenum	112	(59.9)	11	(44.0)	101	(62.4)	
Jejunum	38	(20.3)	5	(20.0)	33	(20.4)	
Ileum	23	(12.3)	6	(24.0)	17	(10.5)	
NOS	14	(7.5)	3	(12.0)	11	(6.8)	
Number of affected metastatic sites							1.00
1	112	(59.9)	15	(60.0)	97	(59.9)	
2	45	(24.1)	6	(24.0)	39	(24.1)	
≥ 3	30	(16.0)	4	(16.0)	26	(16.1)	

NOS = not otherwise specified

The OS was calculated for patients with and without bevacizumab in first-line treatment (table 3). The median OS for patients in whom bevacizumab was added to first-line chemotherapy was 9.3 months, compared to 9.1 months in patients without additional bevacizumab in first-line treatment (p = 0.85) (figure 1). To eliminate the influence of second- and third-line prescription, the OS was also calculated for patients who only received first-line treatment (table 3). The median OS of all patients treated with first-line treatment only was 6.8 months. In the group of patients in whom bevacizumab was added to first-line chemotherapy, the median OS was 8.5 months, compared to 6.4 months in patients exclusively treated with first-line chemotherapy (p = 0.54). In the propensity score matched sample (table 4), identical results were found for the median OS.

In multivariable survival analyses, which were run for the total study population, including use of targeted therapy in first-line therapy, a primary jejunal tumour (HR 0.55, 95% CI 0.36-

0.84) as compared to a primary duodenal tumour was identified as positive prognostic factor for survival in first-line treatment. The use of first-line bevacizumab was no prognostic factor (HR 1.01, 95% CI 0.65-1.59). Also in the propensity score matched sample, the additional use of first-line bevacizumab was no prognostic factor for survival in univariable survival analysis (HR 1.09, 95% CI 0.53-2.26).

Table 2. Univariable logistic regression modelling the odds of additional treatment of bevacizumab in first-line treatment in patients treated with palliative chemotherapy in synchronous metastatic small bowel adenocarcinoma (n = 187).

	Univariable logistic regression	
	OR	(95% CI)
Gender		
Male	1.00	(reference)
Female	0.85	(0.36-1.98)
Age (years)		
<60	1.00	(reference)
60-69	0.68	(0.24-1.90)
≥70	1.06	(0.39-2.89)
Period		
2007-2010	1.00	(reference)
2011-2013	1.03	(0.39-2.74)
2014-2016	0.54	(0.18-1.64)
Location primary tumour		
Duodenum	1.00	(reference)
Jejunum	1.39	(0.45-4.30)
Ileum	3.24	(1.06-9.93)
NOS	2.50	(0.61-10.36)
Number of affected metastatic sites		
1	1.00	(reference)
2	1.00	(0.36-2.75)
≥ 3	1.00	(0.30-3.25)
First-line chemotherapy		
Single-agent	1.00	(reference)
Combination	6.86	(0.90-52.42)

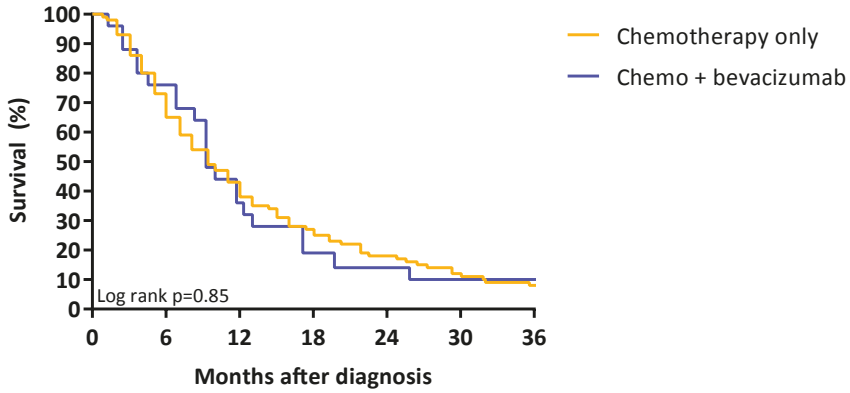
NOS = not otherwise specified, OR = Odds ratio, CI = confidence interval

Table 3. Overall survival of patients with small bowel adenocarcinoma treated with and without additional bevacizumab in first-line treatment.

		Overall survival					
	N	3 months (%)	6 months (%)	9 months (%)	1 year (%)	Median OS (months)	Log rank *p*-value
Total							0.85
First-line chemo	162	87.0	66.1	50.0	38.9	9.1	
First-line chemo + bevacizumab	25	84.0	76.0	52.0	36.0	9.3	
After first-line treatment only							0.54
First-line chemo	120	82.5	55.0	37.5	27.5	6.4	
First-line chemo + bevacizumab	16	75.0	68.8	31.3	25.0	8.5	

Chemo = chemotherapy, OS = overall survival

Figure 1. Survival curve of patients with metastatic disease of small bowel adenocarcinoma, treated with palliative systemic therapy, according to type of prescription in first-line treatment.



	Time to event (months)												
Patients at risk (n)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**
Chemotherapy only	162	141	107	81	63	51	41	30	27	23	17	12	11
Chemo + bevacizumab	25	21	19	13	9	5	4	3	3	2	2	2	2

Chemo = chemotherapy

Table 4. General characteristics of the propensity score matched sample (n = 50).

	Use of bevacizumab in first-line treatment in the propensity score matched sample				
	Yes (n = 25)		**No (n = 25)**		
	N	(%)	N	(%)	*p*-value
Gender					1.00
Male	14	(56.0)	14	(56.0)	
Female	11	(44.0)	11	(44.0)	
Age (years)					0.94
<60	10	(40.0)	10	(40.0)	
60-69	7	(28.0)	8	(32.0)	
≥70	8	(32.0)	7	(28.0)	
Period					0.55
2007-2010	9	(36.0)	6	(24.0)	
2011-2013	10	(40.0)	10	(40.0)	
2014-2016	6	(24.0)	9	(36.0)	
Location primary tumour					0.98
Duodenum	11	(44.0)	11	(44.0)	
Jejunum	5	(20.0)	4	(16.0)	
Ileum	6	(24.0)	7	(28.0)	
NOS	3	(12.0)	3	(12.0)	
Number of affected metastatic sites					0.37
1	15	(60.0)	12	(48.0)	
2	6	(24.0)	11	(44.0)	
≥ 3	4	(16.0)	2	(8.0)	
First-line combination chemotherapy					1.00
Yes	24	(96.0)	24	(96.0)	
No	1	(4.0)	1	(4.0)	

NOS = not otherwise specified

Discussion

The present population-based study is the first to report on the community-based use of targeted therapy in addition to palliative chemotherapy in synchronous metastases of SBA. In 13% of the patients, additional bevacizumab was used to palliative chemotherapy in first-line treatment. Patients with a primary ileal tumour were treated more frequently with bevacizumab in first-line therapy as compared to patients with more proximal tumours. No statistically significant differences in OS were observed after the addition of bevacizumab to palliative chemotherapy after first-line treatment.

The potential beneficial effect of bevacizumab to first-line palliative chemotherapy in synchronous metastatic SBA has only been described in a few reports, including three retrospective studies and one phase II-study. The multicentre, retrospective study of Aydin et al. included 28 patients with advanced SBA, who were treated with FOLFOX or FOLFIRI first-line chemotherapy with (n = 12) and without (n = 25) additional bevacizumab[22]. Toxicity in patients treated with bevacizumab was limited to hypertension (n = 1) and nasal bleeding (n = 1). The reported improvement of median PFS (9.6 vs 7.7 months) and median OS (18.5 vs 14.8 months) after the addition of bevacizumab to first-line combination chemotherapy was not statistically significant.

Two Japanese retrospective studies, conducted by Hirao et al. and Takayoshi et al., included a heterogenous group of patients with advanced SBA, including ampullary tumours and recurrent, non-curatively resected, unresectable or metastatic SBA[20, 21]. In both reports, multiple chemotherapy regimens in first- and second-line therapy were used. Moreover, bevacizumab was prescribed in first-line and for a substantial part beyond first-line therapy. The additional administration of bevacizumab resulted in a median OS of 21.9 months, compared to 11.4 months in the bevacizumab-untreated group of patients. As in both studies all patients treated with bevacizumab in first- and second-line treatment were merged, immortal time biases played a major role in these results and the true value of bevacizumab in first-line treatment could not be established.

The only phase II-study conducted by Gulhati et al. investigated the benefit of additional bevacizumab to combination chemotherapy with CAPOX in 30 patients with advanced SBA (n = 23) and ampullary tumours (n = 7)[19]. Toxicity in patients treated with bevacizumab was limited and included hypertension, fatigue and anorexia. No treatment-related deaths were reported. The median PFS was 8.7 months and the median OS was 12.9 months. The obtained PFS was compared to the PFS of 25 patients with metastatic SBA or ampullary tumours from the prior phase II-study on CAPOX of the same institution, which showed no significant differences[7]. No comparison was made regarding the median OS, although a

higher median OS was described in the prior phase-II study[7].

In the present study, bevacizumab was prescribed in only a limited number of patients in addition to first-line palliative chemotherapy. Probably the rarity of the tumour, the absence of a guideline to treat SBA and the lack of reimbursement of costly targeted therapy for metastatic SBA were all accountable for the low percentage of patients treated with bevacizumab. Bevacizumab was more frequently prescribed to patients with a primary ileal tumour than to patients with more proximal small bowel tumours, which was not observed in the previous mentioned studies. Hypothetically, the historical perspective that distal small bowel tumours behave more like CRC could have influenced clinicians to treat metastatic ileal tumours and metastatic CRC in a similar fashion, with combination chemotherapy and additional bevacizumab[25].

Similar to the treatment of wild RAS-type metastatic CRC, anti-EGFR therapy with panitumumab and cetuximab were increasingly prescribed in second- and third-line treatment in the present study. However, as only 6 patients were treated with anti-EGFR therapy, no conclusions can be drawn on its efficacy. Recently, a small phase-II study assessed the value of anti-EGFR treatment in first-line therapy in metastatic SBA, which showed that panitumumab monotherapy had no clinically beneficial effect in 9 patients with metastatic RAS wild-type SBA[24].

The OS rates for patients receiving palliative chemotherapy with and without bevacizumab in first-line treatment were not statistically significantly different in the present study. However, as the number of patients treated with targeted therapy was low, an obvious non-significant difference in OS could have been clinically relevant, but such a striking difference was not noted. Although study designs differed, the presented results are in line with the study of Aydin et al., who showed non-significant differences in median OS between the groups of patients treated with and without additionally bevacizumab after first-line treatment only[22]. Unfortunately, data on PFS were missing in the current study. However, in the studies of Aydin et al. and Gulhati et al., no significant differences in PFS were found between the groups of patients treated with combination chemotherapy only or with additional bevacizumab[19, 22]. Moreover, as genomic profiling of patients with SBA showed a lower expression of VEGF-A in metastatic disease than in locoregional disease, it seems crucial to identify the subgroup of patients potential benefiting from anti-VEGF therapy[26].

The population-based nature of our data is associated with several risks of potential biases. Data on multiple prognostic factors are lacking, including information on, for instance, extent of disease, disease related symptoms, performance status, comorbidities and the

presence of RAS or BRAF mutations. Moreover, reasons to prescribe chemotherapy or targeted therapy were unknown, duration of systemic therapy was not well documented for all patients, and selection bias could have played a large role. However, as large prospective studies are hard to conduct in the field of this rare disease, the current data are of high value into providing insights into the use and effects of targeted therapy in patients with metastatic SBA in daily practice.

In conclusion, taking into account the limited number of patients receiving first-line bevacizumab and the unknown reasons to prescribe additional targeted therapy, the corresponding survival rates of patients treated with and without additional bevacizumab in first-line treatment, might suggest a limited clinical effect of bevacizumab in addition to first-line palliative chemotherapy on OS. Future research should focus on identifying the subgroup of patients benefiting from anti-VEGF therapy in metastatic SBA.

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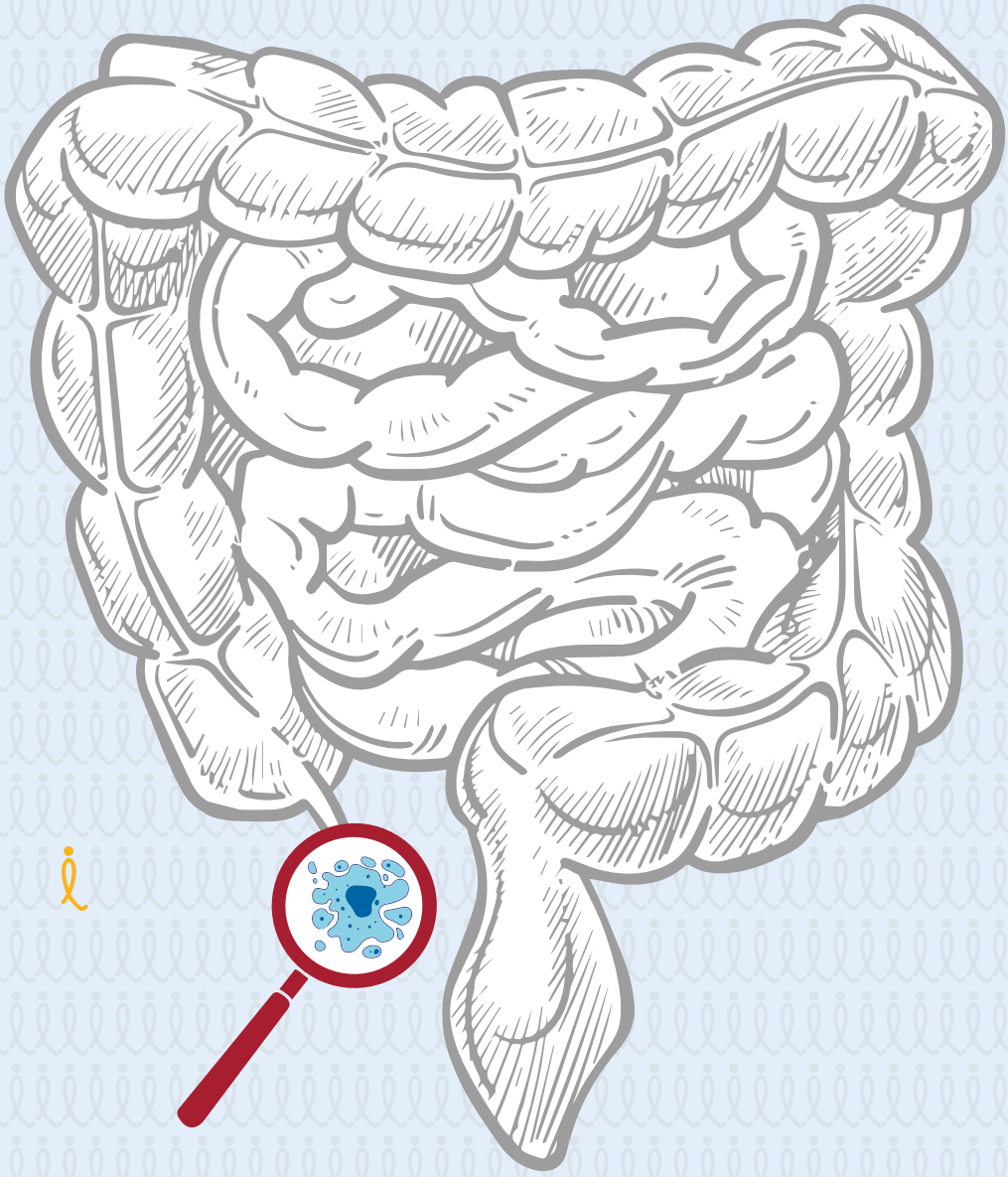
Part III

Histologic subtype in appendiceal cancer



Review: Pathology and its clinical relevance of mucinous appendiceal neoplasms and pseudomyxoma peritonei

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Abstract

Until recently, many classifications existed for the terminology and histopathological classification of appendiceal mucinous neoplasms, mucinous appendiceal adenocarcinomas and pseudomyxoma peritonei (PMP). A major accomplishment was achieved by consensus-based histopathologic classifications on behalf of the Peritoneal Surface Oncology Group International regarding mucinous appendiceal tumors and PMP. As different classification were used over the years and also owing to the rare nature of these tumors, many clinicians are not familiar with the terminology and the impact on patient management. Hence, an overview concerning mucinous appendiceal neoplasms, mucinous appendiceal adenocarcinomas and PMP is provided to serve as an introduction into the basic morphology of these tumors with tentative recommendations for management.

Introduction

Appendiceal epithelial tumors are scarce. In comparison, the incidence of colorectal cancer is approximately 100-fold higher[1]. As appendiceal neoplasms and colorectal cancer exhibit a distinctly different clinical and tumor behavior, these tumors are classified separately in the various tumor classifications[2]. Most appendiceal neoplasms are found during surgery or postoperatively in appendectomy specimens. However, the percentage of appendiceal tumors that is incidentally discovered preoperatively by imaging is increasing over years[3, 4]. A clinical diagnosis is challenging due to a variable symptomatology in patients, ranging from an asymptomatic course to vague acute or chronic abdominal complaints, even with symptoms mimicking acute appendicitis[4-6].

Pathology is of prognostic significance in patients with appendiceal cancer[2]. Adenocarcinoma is the most common histologic malignant subtype, accounting for more than half of the cases[6-8]. Other malignant subtypes of appendiceal cancer include lymphomas, sarcomas, grade 1 and 2 neuroendocrine tumors (NETs) and goblet cell tumors/carcinomas (previously called goblet cell carcinoids)[3, 6]. Goblet cell tumors are a remarkable group of tumors, occurring almost exclusively in the appendix. Recent insights have shown that goblet cell tumors are lesions composed of several cell types, including neuroendocrine cells, Paneth cells and goblet cells. These tumors show a continuum with adenocarcinomas, and the prognosis is dependent of the dominant morphologic component of the goblet cell tumor[9, 10].

A subgroup of epithelial tumors, including those with uncertain malignant potential and adenocarcinomas, are known for their extensive mucus production and therefore, belong to the group of mucinous appendiceal neoplasms. Mucinous appendiceal neoplasms are the leading cause of pseudomyxoma peritonei (PMP), a unique clinical condition characterized by progressive accumulation of mucinous ascites and peritoneal implants with fatal outcome[1, 11-13]. The terminology and histopathological classification of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and PMP has been subject to diverse consensus-based changes over time. The aim of this general overview is to provide an introduction into the basic morphology of these tumors with tentative recommendations for management of these various neoplasms.

Pathology

Mucinous appendiceal neoplasms are a frequently discussed item within the group of appendiceal tumors, but the classification might still be experienced as confusing by clinicians[9-11, 13-18]. Mucinous appendiceal neoplasms are distinguished in 3 different categories according to the latest consensus-based classification by the Peritoneal Surface Oncology Group International (PSOGI), consisting of true premalignant lesions, tumors of uncertain malignant potential, and malignant lesions[13, 16]. Serrated polyps and tubular, villous, and tubulovillous adenomas all belong to the group of premalignant lesions. Meanwhile, tumors of uncertain malignant potential, also known as low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs), share some histologic features with adenomas, but these lesions have the capacity to proliferate out of the appendix in a malignant fashion. Finally, the malignant lesions can be subdivided into mucinous adenocarcinomas, with or without a signet ring cell component, and signet ring cell carcinomas. The premalignant lesions do not have the potential to cause PMP, which is not the case for the other 2 categories[11, 19].

LAMN

A subgroup of mucinous appendiceal lesions can be classified as LAMNs. Historically, cystadenoma and mucocele were used as synonyms for LAMN, but these terms were abandoned based on consensus, owing to their incomplete and misleading nature[10, 11, 13, 15]. The histologic criteria for LAMN are summarized in table 1. The most important and distinctive feature of LAMN is the low-grade cytologic atypia without signs of invasive infiltration in the appendiceal wall. In almost all cases of LAMN, there is loss of the normal mucosal architecture of the appendix, at least focally, with loss of the lamina propria and muscularis mucosa with lymphoid follicle atrophy associated with fibrosis of the submucosa[16]. LAMNs are the main cause of PMP. These lesions generally do not cause nodal or distant extraperitoneal metastases[13].

In case of a suspected LAMN, accurate pathologic examination of the total appendix is essential, as some features are associated with potential intraperitoneal tumour spread, which worsens the natural disease course and the prognosis of the patient. Worrisome features of LAMN include appendiceal rupture (including micro-perforation), a background of appendiceal inflammation, the presence of extra-appendiceal mucin, or extensive dissecting mucin pools within the appendiceal wall. LAMNs with these ominous features are prone to develop into PMP[4, 13, 20, 21]. A LAMN in an intact appendix and without other risk factors is considered as benign with only very small risk to evolve to PMP.

Patients with LAMN show different characteristics, clinical course, and survival than patients

with a mucinous adenocarcinoma. Patients are generally young, with a median age of approximately 53 years, and with a slightly female predominance (~60%)[15, 20, 22]. Among all mucinous appendiceal neoplasms without peritoneal spread, it has the most favorable prognosis. In patients with completely resected LAMNs or with low-volume peritoneal disease, a 5-year recurrence-free survival and overall survival rate of 95.2% and 100% were observed[23].

Table 1. Classification and grading of mucinous epithelial lesions of the appendix Adapted from Carr et al.[13]

Terminology	Grading	Histologic features
Serrated polyp	No grade dysplasia	Lesion with serrated featured, confined to the mucosa and intact muscularis mucosae. In case of dysplasia, it can be classified as low or high grade.
Adenoma	Low/high grade dysplasia	Adenoma with tubular, tubulovillous of villous features, resembling usual colorectal type. Confined to mucosa and intact muscularis mucosae.
LAMN	Low	Mucinous neoplasm with low-grade cytologic atypia and without invasive infiltration but with any of the following features: • loss of muscularis mucosae • fibrosis of submucosa • 'pushing invasion' (expansile or diverticulum-like growth) • dissection of acellular mucin in the appendiceal wall • undulating or flattened epithelial growth • rupture of the appendix • mucin and/or cells outside the appendix
HAMN	High	Mucinous neoplasm with the architectural features of LAMN but with high-grade cytologic atypia.
Mucinous adenocarcinoma	Well/ moderately/ poorly differentiated	Mucinous neoplasm, comprising of >50% extracellular mucin, with infiltrative invasion.
Mucinous adenocarcinoma with signet ring cells	Poorly differentiated	Mucinous adenocarcinoma, comprising up to 50% signet ring cells
Signet ring cell adenocarcinoma	Poorly differentiated	Adenocarcinoma, comprising of >50% signet ring cells

LAMN = low-grade appendiceal mucinous neoplasm, HAMN = high-grade appendiceal mucinous neoplasm.

HAMN

The term HAMN was added in the latest classification for mucinous neoplasms, but these tumors are extremely rare and therefore still poorly understood[13]. These lesions display the same architectural features of a LAMN but with high-grade cytology (table 1)[13, 16]. It might be hypothesized that HAMNs form an intermediate group between LAMNs and mucinous adenocarcinomas. In a small study by Misdraji et al HAMNs had a more aggressive clinical course than LAMNs[15]. Information on prognosis is lacking for patients with HAMNs.

Mucinous adenocarcinoma (including signet ring cell adenocarcinoma)

Appendiceal mucinous adenocarcinomas are defined as mucinous neoplasms comprised of >50% extracellular mucin, with the presence of infiltrative invasion of the appendix.[13, 16] According to the PSOGI classification, mucinous adenocarcinomas are classified as well, moderately, and poorly differentiated, although the histologic criteria for the different grading systems are not well-established[13]. The presence of signet ring cells in the lesion to whatever extent, indicates a poorly differentiated carcinoma. If more than 50% of the tumor consists of signet ring cells, the term signet ring cell carcinoma is used. Otherwise, if less than 50% of the cells have signet ring cell morphology, the tumor is classified as poorly differentiated adenocarcinoma with signet ring cells[13].

Mucinous adenocarcinomas develop mainly from precursor lesions[10, 12]. Patients are generally young, with a median age of 50 to 60 years, and many patients already present with synchronous metastatic disease, especially in the case of signet ring cell adenocarcinomas[2, 24, 25]. Nodal metastases are commonly seen, in contrast to patients with LAMNs. Mucinous and signet ring cell adenocarcinomas metastasize intra- and extraperitoneally, but usually intra-abdominal dissemination occurs first. Survival is strongly dependent of histological grade[2, 12, 24, 26]. Among appendiceal adenocarcinomas, mucinous adenocarcinoma has the most favorable prognosis, with a median overall survival of over 60 months. Like colorectal cancer, patients with signet ring cell appendiceal adenocarcinoma have the worst overall survival among all morphologies, with a reported median overall survival of approximately 20 to 25 months and a 5-year survival rate of 22% to 38%[2, 8, 12, 24].

Peritoneal disease

PMP is a heterogeneous clinical disease, for which a uniform and comprehensive definition is still lacking. It is distinguished from usual peritoneal metastases of other gastrointestinal cancers by the presence of excessive amounts of mucin in the peritoneal cavity[11]. However, as the extent of mucinous ascites to be classified as PMP is not clarified, the exact cutoff point between (mucinous) peritoneal metastases and PMP is unclear. As already stated by Carr et al, PMP should only be used for the macroscopic appearance of mucinous ascites, as it is not a histologic diagnosis[11]. Mucinous appendiceal neoplasms are the leading cause of PMP[13].

PMP can be divided into several categories based on histologic features of the peritoneal disease with its clinical consequences and prognostic value, including acellular PMP, low-grade PMP, high-grade PMP and high-grade PMP with signet ring cells. It is of importance to describe and subdivide the histologic grade of both peritoneal disease and the primary tumor, as morphology can be discordant in rare cases. For instance, patients with LAMN may present with high-grade PMP, whereas invasive adenocarcinomas could cause low-grade PMP. This discordance may in some cases be explained by sampling error or incorrect diagnosis. However, the histologic grade of the peritoneal disease outweighs its primary appendiceal lesion in terms of prognosis[11, 13, 27].

Acellular PMP

The separated entity of acellular mucin in the overarching group of PMP is characterized by the absence of epithelial cells in the mucin within the peritoneal cavity. In case of appendiceal origin, this acellular mucin usually results from LAMNs with low-volume peritoneal disease, mostly located in the right lower quadrant of the abdomen[22]. Patients with acellular mucin comprise a small group within the spectrum of PMP and have the most favorable clinical outcome, owing to the relatively indolent course of disease[15, 22].

Low-grade PMP

Low-grade PMP is the most common variant of PMP. Other terms used for low-grade PMP are low grade mucinous carcinoma peritonei and disseminated peritoneal adenomucinosis (DPAM)[11]. All histologic features associated with low-grade PMP are described in table 2. The main cause of low-grade PMP are LAMNs[27].

Table 2. Classification of pseudomyxoma peritonei. Adapted from Carr et al.[11, 13]

Terminology	Histologic features
Acellular PMP	Mucin within the peritoneal cavity without neoplastic epithelial cells
Low-grade PMP	• Low-grade or minimal cytologic atypia • Epithelial component typically scanty • Strips, gland-like structures or small clusters of cells • Not more than occasional (sporadic) mitoses • 'Pushing' invasion into underlying organs
High-grade PMP	• High-grade cytologic atypia • High cellularity • Cribiform growth • Numerous mitoses • Destructive infiltrative invasion of underlying organs
High-grade PMP with signet ring cells	Any lesion with a component of signet ring cells

PMP = pseudomyxoma peritonei

High-grade PMP

Peritoneal disease with high-grade cytologic atypia is also known in literature as high-grade mucinous carcinoma peritonei, peritoneal mucinous carcinomatosis (PMCA) and high-grade PMP. High-grade PMP is in the majority of cases caused by mucinous adenocarcinomas[11, 13]. Further details are listed in table 2. It remains to be seen whether HAMNs will cause high or low-grade PMP or even an intermediate form. A continuum is present between high-grade PMP and non-mucinous peritoneal metastases in which the presence of a large amount of mucin points to PMP instead of non-mucinous peritoneal metastases[11].

High-grade PMP with signet ring cells

High-grade PMP with signet ring cells is classified separately from high-grade PMP without signet ring cells, as the presence of signet ring cells is a powerful negative prognostic factor for survival in patients with PMP[12, 13]. All further criteria for high-grade PMP also apply for high-grade PMP with signet ring cells.

Management

LAMN

For patients without extra-appendiceal disease, appendectomy and follow-up is recommended. Right hemicolectomy should not be performed, because it provides no survival benefit for patients with LAMNs, as these lesion usually do not cause nodal metastases[12, 28]. In patients with positive margins, additional surgery like cecectomy may be considered, although several data suggest no survival benefit after further resection[4, 29]. Although the exact duration and prognostic value of follow-up is unknown, long-term follow-up of 5 to 10 years is recommended, because peritoneal dissemination can occur lately after the primary lesion[13, 16]. Currently, follow-up is recommended to start annually, including an abdominal computed tomography (CT) scan and determination of serum tumour markers (carcinoembryonic antigen, cancer antigen 19.9, and cancer antigen-125)[13]. Especially in patients with worrisome prognostic signs, such as elevated tumour markers, positive resection margins or the presence of mucin beyond the appendix, close and extended follow-up is advised[13, 20]. Whether patients with a radically resected and intact appendix with LAMN without worrisome features need close and frequent follow-up is debatable, as it is considered as a lesion with an indolent behaviour and a low potential to develop PMP[4]. In the study of Guaglio et al, a 5-year recurrence-free rate of 95.2% and no patient deaths were found in patients with radically resected LAMNs or low-volume peritoneal disease[23].

HAMN

As the term HAMN was introduced recently, limited literature regarding the management of this lesions is present. Moreover, the diagnosis HAMN is exclusively made after surgery by pathological examination of the appendix, in which the surgeon has already performed an appendectomy, cecectomy or right hemicolectomy. Due to the rareness of the tumour, it is still unknown whether local removal of the tumour is sufficient or a more extended tumour resection is needed. Long-term follow-up is advised, since patients with HAMNs might have an increased risk to develop peritoneal disease[16].

Mucinous appendiceal adenocarcinoma

In patients with mucinous adenocarcinomas, a right hemicolectomy with lymph node dissection should be performed in locoregional disease, due to an increased risk of lymph node invasion and improved survival rates compared with appendectomy only[12, 21, 30]. The value of adjuvant chemotherapy is unknown, as no randomized controlled trials have been conducted due to the rarity of the appendiceal adenocarcinomas. In a retrospective cohort study of Asare et al, the role of adjuvant systemic therapy on overall survival was evaluated and showed a survival benefit for treated patients with mucinous and non-mucinous morphology[25]. However, in this study, information about the systemic regimens used were

lacking, and adjuvant chemotherapy was administrated in all locoregional stages (I-III). In all patients with appendiceal mucinous adenocarcinomas, follow-up is recommended according to the guidelines of colorectal cancer, because recurrence and distant metastases are frequently observed, comparable with other gastrointestinal mucinous adenocarcinomas[13].

Peritoneal disease

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC)

In peritoneal dissemination, CRS+HIPEC is recommended for all types of PMP, although different criteria apply for low- and high-grade PMP. For all peritoneal malignancies, the extent of the peritoneal disease is assessed by the peritoneal cancer index (PCI). The PCI comprises a score between 1 to 39, composed of a scoring system in which the peritoneal cavity and small bowel are divided in 13 regions, in which the tumour burden is assessed through a score of 1 to 3[31]. For example, in peritoneal metastases of colorectal origin, CRS+HIPEC is usually not performed if PCI ≥20, as radical resection of the peritoneal tumour is nearly impossible and the morbidity caused by CRS+HIPEC outweighs the potential minimal beneficial effect on survival[32].

In patients with low-grade PMP, CRS+HIPEC should always be considered irrespective of the PCI. If complete cytoreduction could be achieved, CRS+HIPEC is still a curative option in patients with high peritoneal tumour load[1, 33, 34]. The great impact of CRS+HIPEC on survival in low-grade PMP is reflected in a reported median overall survival of 7.7 to 12.3 years, and a 5-year and 10-year survival rate of 84% and 48%, respectively, in case of complete cytoreduction[1, 26, 27, 35]. In case of incomplete cytoreduction, the 5-year survival rate decreased to 63%[27]. Even in patients with very extensive disease with a PCI ranging from 31 to 39, long term survival was achieved with 5- and 10-year survival rates of 73% and 68%, respectively, in the study of Chua et al[1]. These results might indicate an increased survival for a selected group of patients, if referred to a specialized center[1].

In contrast, the PCI may be considered to select patients with high-grade PMP for CRS+HIPEC, as a high PCI is associated with significant poorer survival. After achieving complete cytoreduction, a median overall survival of 2.8 to 5.3 years, and a 5-year and 10-year survival rate of, respectively, 48% and 40% are reported[1, 26, 27, 35, 36]. However, after incomplete cytoreduction the 5-year overall survival decreases to only 23%[27].

CRS+HIPEC can be considered in patients with high-grade PMP with signet ring cells, although a positive impact of CRS+HIPEC on survival is less clear. Several studies showed a poor prognosis after CRS+HIPEC for patients with high-grade PMP with signet ring cells, with a median overall survival of only 9 to 31 months and a 5-year survival rate varying from

0 to 22%[26, 35, 36]. As patient selection by clinicians already occurred in these studies, the use of CRS+HIPEC for high-grade PMP with signet ring cells might be limited in daily practice, especially given the small gain in survival and the major morbidity up to 50% in treated patients caused by CRS+HIPEC[26, 30].

Systemic therapy

Neo-adjuvant setting

Several studies investigated the effect of neo-adjuvant chemotherapy prior to CRS+HIPEC. Only in the study of Milovanov et al, in a small group of 18 patients with high-grade PMP with signet ring cells, a benefit in progression-free survival and overall survival were observed with preoperative systemic therapy, followed by complete cytoreduction[37]. However, it should be noticed that many different chemotherapeutic regimens and targeted therapies were used[37]. No other studies found a survival gain for patients treated with neo-adjuvant or perioperative chemotherapy in low- or high-grade PMP[1, 38-43].

Adjuvant setting

No evidence exists for a beneficial effect of the subsequent use of adjuvant systemic therapy after CRS+HIPEC in patients with PMP of any type[40, 44].

Palliative setting

Palliative systemic therapy can be considered in patients with irresectable or recurrent (high-grade) PMP, who are not suitable for CRS+HIPEC. Generally accepted reasons for surgical ineligibility include short progression-free survival (often <1 year to prior CRS+HIPEC), residual disease after prior CRS+HIPEC, and extensive comorbidities[45, 46]. No randomized controlled trials have been performed for palliative systemic therapy in patients with PMP. Commonly, chemotherapy regimens by analogy of colorectal cancers are used, like fluoropyrimidine-based regimens, either fluorouracil/ capecitabine monotherapy, or oxaliplatin- or irinotecan-based combination therapy[41, 46]. In the series of Choe et al., addition of targeted therapy to palliative chemotherapy was used in 50% of the cases, mainly with a doublet chemotherapeutical regimen[45]. Owing to the rarity of the tumour, most of the performed studies were of retrospective design and conducted in the same single tertiary institution. Besides, different patient inclusion criteria and chemotherapy regimens were used in most studies.

Despite different regimens used in diverse studies, it was suggested that palliative systemic therapy could provide a survival benefit in selected patients not suitable for CRS+HIPEC. In the treated group of patients, the median progression-free survival and median overall survival was around 8 months and 26 to 56 months, respectively[41, 46-48]. Overall response rate

(ORR) varied between 20% and 60%, depending on the definition of ORR and the regimens used[41, 46-48]. The use of the biologic agent bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) antibody, in 95% of the cases in addition to combination chemotherapy, was associated with an ORR of 87% and a gain in progression-free and overall survival in a selected group of patients of 5 months and 34 months, respectively[45].

Among patients treated with palliative chemotherapy, a moderately to poorly differentiated tumour, including signet ring histology, was associated with poorer survival than patients with a well-differentiated tumour, which reflects the more aggressive biological behaviour of the higher grade tumors[46]. However, the administration of palliative chemotherapy provides a benefit in progression-free survival and overall survival for selected patients with high-grade PMP. In these patients, with primary moderately or poorly differentiated tumours (including signet ring cells), the overall survival improved for moderate and poor differentiation from 20 to 36 months and 12 to 19 months, respectively[25]. The use of anti-VEGF therapy was associated with prolonged progression-free survival and overall survival in all histologic subtypes, but especially in high-grade PMP[45]. Although the number of patients included in the studies were small and selection bias probably played a significant role, these results favour the use of palliative chemotherapy and targeted therapy in selected patients with irresectable or recurrent high-grade PMP.

Patients with low-grade PMP derive less to no benefit from palliative chemotherapy compared to higher grade tumors[25, 45]. Asare et al. even showed a worse overall survival for patients treated with palliative chemotherapy compared with non-treated patients[25]. A clinical relevant gain of 7 months in progression-free survival was observed in patients with low-grade PMP after the administration of anti-VEGF therapy[45]. Perhaps this might indicate a role for this targeted agent in symptomatic patients with low-grade PMP not suitable for CRS+HIPEC. However, the generally indolent behaviour of irresectable or recurrent low-grade PMP challenges both clinicians and patients to decide between an active management or observation.

Discussion

The classification and nomenclature of mucinous appendiceal neoplasms and PMP have been adapted several times over the years[11, 13]. However, these classifications are based on experiences and theoretic assumptions of experts in the field, and are not totally evidence-based. Future research is needed to determine the accuracy and clinical relevance of the most recent consensus-based classification.

Despite the increased knowledge and insights concerning appendiceal mucinous neoplasms in recent years, there is still much to be investigated and clarified. For instance, exact information on the incidence and natural course of LAMNs and HAMNs is lacking. Besides, it is difficult to distinguish between the true benign and the premalignant lesions with its potential to cause PMP within the subgroup of LAMNs, which might affect management and surveillance decisions. Especially the subgroup of HAMNs is currently poorly understood, as this subgroup is extremely rare, and it is unknown whether the biological behaviour differs significantly from other subgroups, also in their potential to cause peritoneal disease[13, 16].

No strict guidelines exist for the management of mucinous appendiceal neoplasms, especially LAMNs and HAMNs, and PMP. In patients with PMP, CRS+HIPEC should be considered in all types of PMP, taking the potential benefits and harms into account for the histologic subtypes[1, 26, 27, 33-36]. For instance, in patients with the aggressive high-grade PMP with signet ring cells, the value of CRS+HIPEC is limited. However, selected patients could still have a clinical benefit from CRS+HIPEC in high-grade PMP with signet ring cells, but this has to be studied in a larger subset of patients.

There seems to be no indication for standard neo-adjuvant or adjuvant systemic therapy in PMP. However, it is theoretically possible that selected high-grade PMP patients with irresectable disease due to a high degree of tumour burden could benefit from neo-adjuvant chemotherapy[1, 38-44]. On an individual level, the administration of neo-adjuvant chemotherapy could result in a situation of resectable peritoneal disease, after which CRS+HIPEC could be performed. Palliative systemic therapy can be considered in patients with irresectable or recurrent PMP, especially in high-grade PMP patients. The administration of palliative chemotherapy could result in a prolonged survival in high-grade PMP patients, but probably not in patients with low-grade PMP[25, 41, 46-48]. There are indications that both low- and high-grade PMP patients could possibly benefit from the use of targeted therapy[45]. However, it should be noted that the obtained evidence on patient management is mainly based on the experience of a few tertiary centres.

Moreover, the present insights into appendiceal mucinous neoplasms including LAMNs

are largely derived of collected samples by hospitals and pathology archives[20]. Data on lesions that were previously assumed to be non-malignant lesions are usually not recorded by cancer registries. For example, in the Netherlands Cancer Registry only in case of PMP, data on the primary appendiceal lesions as LAMNs and HAMNs are registered. In addition, due to the new classification of mucinous appendiceal neoplasms, the available data of these tumours might be contaminated, as some LAMNs were probably classified as well-differentiated mucinous adenocarcinomas, resulting in incorrect survival rates in retrospective or population-based studies. However, if collected properly, population-based data could be of value for future research in reflecting the clinical course of the disease and the use and effect of treatments in daily practice.

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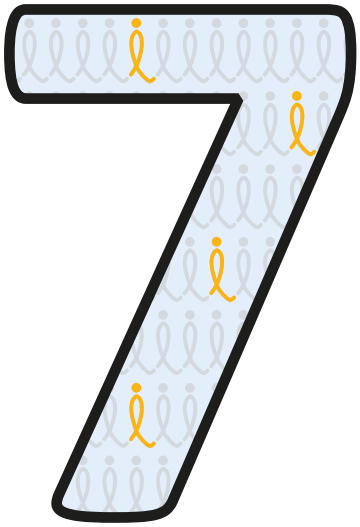

The prognostic relevance of histologic subtype in appendiceal adenocarcinoma

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Abstract

Background: The aim of this population-based study was to determine the prognostic value of the histologic subtypes mucinous (MAC), non-mucinous (AC) and signet ring cell (SRCC) adenocarcinoma among patients with appendiceal cancer.

Methods and materials: Data from the Netherlands Cancer Registry (NCR) of patients with primary appendiceal adenocarcinomas with MAC, AC and SRCC histologic subtype, diagnosed between 2001-2015 were used (n = 675). To categorize patients according to the recent histopathological classification, the NCR was linked with the Dutch Pathology Registry (PALGA). Log-rank tests and Kaplan-Meier analyses were performed to estimate overall survival (OS), and the cox proportional hazards model was run to identify prognostic factors.

Results: AC was the most frequently encountered histologic subtype (50.9%), followed by MAC (35.8%) and SRCC (13.3%). In locoregional disease, histologic subtype was not a prognostic factor for OS with 5-year survival rates for patients with AC, MAC and SRCC of 60.0%, 60.5% and 69.6% respectively ($p = 0.68$). Metastatic disease was more common in SRCC (53.8%) than in MAC (38.8%) and AC (23.4%) ($p < 0.0001$). Median OS for patients with metastatic disease was 12.6, 27.7 and 18.2 months in AC, MAC and SRCC respectively ($p < 0.005$). MAC was associated with higher survival compared to AC (HR 0.48, 95% CI 0.34-0.69). In subanalyses, MAC was only a positive prognostic factor compared to AC in patients with peritoneal metastases (HR 0.42, 95% CI 0.28-0.62).

Conclusion: Histologic subtype had no prognostic relevance in locoregional or systemic metastatic disease in appendiceal adenocarcinoma. In peritoneal metastases, mucinous histologic subtype was a favourable prognostic factor, compared to non-mucinous and signet ring cell subtype.

Introduction

Appendiceal epithelial tumours are rare, and are mostly incidentally found in appendectomy specimens[1]. The most frequently encountered malignant subtype within the group of appendiceal neoplasms is the adenocarcinoma[2-4]. Appendiceal adenocarcinomas are subdivided into the mucinous, non-mucinous and signet ring cell subtype[1, 3]. The histologic subtype is thought to be of significant relevance in appendiceal adenocarcinomas, as earlier research revealed that patients with a mucinous appendiceal adenocarcinoma have a better or comparable outcome, compared to non-mucinous adenocarcinomas, depending on the stage of disease[1-3, 5].

However, up until recently the definition of a mucinous appendiceal adenocarcinoma has not been universal, as different histopathological criteria and classifications for mucinous appendiceal neoplasms existed[6-10]. Recently, a consensus-based histopathological classification regarding mucinous appendiceal neoplasms and pseudomyxoma peritonei (PMP) was published on behalf of the Peritoneal Surface Oncology Group International (PSOGI)[11]. With this classification, appendiceal mucinous neoplasms, including the low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasms (HAMN) and mucinous appendiceal adenocarcinoma, can be classified with internationally corresponding definitions, based on well-defined criteria.

As universal and clear definitions for mucinous appendiceal neoplasms were previously lacking, it could be possible that prognostically favourable LAMNs and HAMNs were incorrectly classified as mucinous appendiceal adenocarcinomas. Therefore, it was the aim of the present population-based study to determine the prognostic value of histologic subtype more accurately, by using the new consensus-based histopathological classification, in a subset of patients with mucinous, non-mucinous and signet ring cell adenocarcinomas in The Netherlands between 2001 and 2015.

Material and Methods

Data collection

Data were drawn from the Netherlands Cancer Registry (NCR). The NCR collects population-based data on all newly diagnosed malignancies of all Dutch citizens and covers an area of approximately 17 million inhabitants. Primary source of notification of the NCR is the automated nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses[12]. Specially trained administrators of the NCR routinely extract information on patient and tumour characteristics, diagnosis and treatment from the medical records. In the NCR, all primary tumours are staged according to the Tumour Node Metastasis (TNM) classification. In case the pathological data is missing, the clinical TNM stage is used. The topographical site of the primary tumour and systemic metastases are registered according to the third version of the International Classification of Disease for Oncology (ICD-O). Unfortunately, the exact topographical metastatic site was not collected until 2008 in some regions of the NCR.

All consecutive patients diagnosed with primary appendiceal adenocarcinomas (ICD-O code C18.1) between 2001 and 2015 were included in this study. Appendiceal adenocarcinomas were classified into mucinous (morphology codes 8470, 8480 and 8481), non-mucinous (morphology codes 8140, 8141, 8144, 8145, 8210, 8211, 8255, 8260, 8261, 8262, 8263, 8440, 8460, 8560, 8570 and 8574) and signet ring cell adenocarcinomas (morphology code 8490).

As multiple tumour classifications of appendiceal mucinous neoplasms existed over time, the group of formerly classified mucinous appendiceal adenocarcinomas could be contaminated. Therefore, the pathological reports, including macroscopy and microscopy reports, of patients with appendiceal mucinous adenocarcinomas with morphology codes 8470 and 8480, in which cystadenomas and LAMNs, HAMNs or PMP may have been included, were retrospectively revised through linkage with PALGA (n = 424). The first revision of the pathological reports was performed by LL, and afterwards checked and revised by CH. The histologic subtype was retrospectively adjusted for the patients concerned, according to the most recent histopathological classification for mucinous appendiceal neoplasms [11].

For the present study, patients with LAMNs, HAMNs, clinical or pathological confirmed PMP without confirmed appendiceal mucinous adenocarcinomas as origin and patients with an unknown tumour stage, were excluded from further analyses. A distinction between locoregional ($T_{1-4}N_{0-2}M_0$) and metastatic disease ($T_{1-4}N_{0-2}M_1$) was made to evaluate the prognostic relevance of histologic subtype according to primary stage. In metastatic disease,

the metastatic sites retroperitoneum and peritoneum (C48), connective, subcutaneous and other soft tissues of abdomen (C49.4) and ovaries (C56) were defined as peritoneal metastases. All other metastatic sites were coded as systemic metastases.

Vital status of patients at 31 January 2019 was assessed through linkage of the NCR with civil municipal registries and the central bureau for genealogy, which collects data on all deceased inhabitants of the Netherlands. Survival was calculated on all-cause mortality.

Statistical analysis

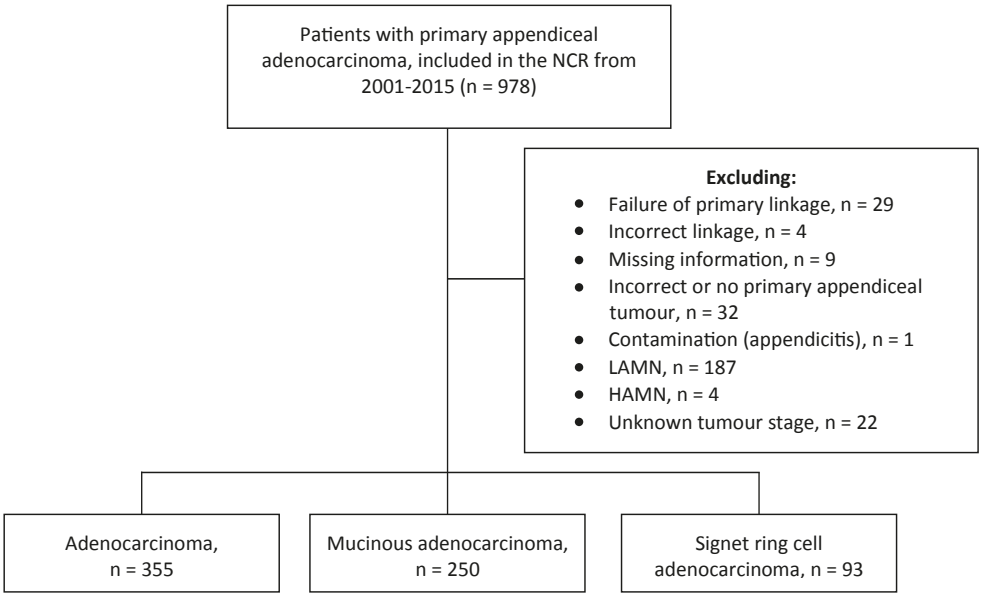
Descriptive statistics were used to provide an overview of the patient and tumour characteristics. Differences in patient and tumour characteristics were analysed with a two-sided chi-square test. Survival time was defined as the time from the date of diagnosis to death or last follow-up date for patients who were lost to follow-up or still alive at 31 January 2019. Survival was estimated with the log-rank test and Kaplan-Meier analyses. Multivariable survival analyses, using the Cox proportional hazards model, were run to identify independent prognostic factors of overall survival. To evaluate the prognostic impact of metastatic site, the subgroups peritoneal and systemic metastases were created. Patients with both peritoneal and systemic metastases, were analysed in both subgroups, corrected for several clinical prognostic factors. Potential clinical prognostic factors for which was corrected, included gender, age, period of diagnosis and treatment. The tumour related treatment strategies for which was corrected, included surgery for both the primary tumour and metastatic sites, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC), systemic therapy (chemotherapy + targeted therapy), radiotherapy and other palliative interventions. Hazard ratios (HRs) were presented with 95% confidence intervals (CIs).

The statistical package SAS Statistical Software (version 9.4, SAS Institute, Cary, NC, USA) was used for the analyses. For all statistical tests, a two-sided p-value of $p < 0.05$ was considered as statistically significant.

Results

The current study included 986 patients diagnosed with an appendiceal adenocarcinoma between 2001 and 2015. After revision of the pathological reports of patients initially diagnosed or classified with mucinous appendiceal adenocarcinomas, 264 patients were excluded due to failure of primary linkage (n = 29), incorrect linkage (n = 4), missing information (n = 9), incorrect primary tumours or no primary appendiceal tumour, (n = 32), contamination of the results due to appendicitis (n = 1), and a primary LAMN (n = 187) or HAMN (n = 4). Thereafter, patients with an unknown tumour stage were excluded (n = 22), remaining 698 patients, including 355 patients with (non-mucinous) adenocarcinoma, 250 with mucinous appendiceal adenocarcinoma and 93 with the signet ring cell subtype (figure 1).

Figure 1. An overview of the included patients with primary appendiceal adenocarcinoma diagnosed between 2001 and 2015 in the Netherlands.



Study population

Among the histologic subtypes, significant differences were noted according to stage of disease at the time of diagnosis. Patients with signet ring cell adenocarcinoma (SRCC) presented with metastatic disease in 53.8% of the cases, compared to 38.8% and 23.4% in patients with primary mucinous adenocarcinoma (MAC) and non-mucinous adenocarcinoma

(AC) respectively (p < 0.0001).

In locoregional disease, patients with a primary MAC were more frequently female (56%), whereas in SRCC a male preference (65%) was noted (p < 0.05). Median age was comparable for the histologic subtypes in locoregional disease, and was between 67 and 70 years old. Further details of patients with locoregional disease are shown in table 1. In metastatic disease, there was a significantly female predominance in all histologic subtypes (66-76%). Median age in metastatic disease was between 62 and 64 years old. Details on other patient- and tumour characteristics for metastatic disease are listed in table 2.

Table 1. General characteristics of patients with non-mucinous, mucinous and signet ring cell appendiceal adenocarcinoma in locoregional disease (n = 468).

	Non-mucinous adenocarcinoma (n = 272)		**Mucinous adenocarcinoma (n = 153)**		**Signet ring cell adenocarcinoma (n = 43)**		
	N	(%)	N	(%)	N	(%)	*p*-value
Gender							< 0.05
Male	139	(51.1)	67	(43.8)	28	(65.1)	
Female	133	(48.9)	86	(56.2)	15	(34.9)	
Age (years)							0.31
< 60	78	(28.7)	41	(26.8)	15	(34.9)	
60-69	77	(28.3)	38	(24.8)	6	(14.0)	
≥ 70	117	(43.0)	74	(48.4)	22	(51.2)	
Stage							0.10
1	77	(28.3)	26	(17.0)	8	(18.6)	
2	140	(51.5)	91	(59.5)	26	(60.5)	
3	55	(20.2)	36	(23.5)	9	(20.9)	
Period							0.54
2001-2005	94	(34.6)	52	(34.0)	10	(23.3)	
2006-2010	77	(28.3)	46	(30.1)	17	(39.5)	
2011-2015	101	(37.1)	55	(36.0)	16	(37.2)	

In metastatic disease, the most commonly affected metastatic site was the peritoneum (89%), including ovarian involvement, followed by the liver (16%). Peritoneal dissemination was significantly more common in MAC (97%) and SRCC (94%) than in AC (77%) (p < 0.0005). Ovarian metastases as a part of peritoneal dissemination, were more frequent in MAC (36%) and SRCC (35%) than in AC (16%) (p = 0.01). Metastases confined to the peritoneal cavity, which may include the ovaries, but without other systemic metastases, were present in 64% of patients with AC, and in 81% and 85% of the patients with MAC and SRCC respectively (p = 0.01). Liver metastases were more frequently encountered in AC (29%) than in MAC (13%) or SRCC (2%) (p < 0.0005).

Table 2. General characteristics of patients with non-mucinous, mucinous and signet ring cell appendiceal adenocarcinoma in metastatic disease (n = 230).

	Non-mucinous adenocarcinoma (n = 83)		Mucinous adenocarcinoma (n = 97)		Signet ring cell adenocarcinoma (n = 50)		
	N	(%)	N	(%)	N	(%)	*p*-value
Gender							0.32
Male	28	(33.7)	24	(24.7)	12	(24.0)	
Female	55	(66.3)	73	(75.3)	38	(76.0)	
Age (years)							0.57
< 60	34	(41.0)	42	(43.3)	21	(42.0)	
60-69	23	(27.7)	27	(27.8)	19	(38.0)	
≥ 70	26	(31.3)	28	(28.9)	10	(20.0)	
Period							0.37
2001-2005	21	(25.3)	24	(24.7)	7	(14.0)	
2006-2010	27	(32.5)	37	(38.1)	17	(34.0)	
2011-2015	35	(42.2)	36	(37.1)	26	(52.0)	
Number of affected metastatic sites*							0.15
1	48	(65.8)	41	(47.7)	23	(47.9)	
2	16	(21.9)	27	(31.4)	17	(35.4)	
≥ 3	9	(12.3)	18	(20.9)	8	(16.7)	
Peritoneal metastases (including ovarian)*							< 0.0005
Yes	56	(76.7)	83	(96.5)	45	(93.8)	
No	17	(23.3)	3	(3.5)	3	(6.3)	
Ovarian metastases*							0.01
Yes	12	(16.4)	31	(36.1)	17	(35.4)	
No	32	(83.6)	55	(64.0)	31	(64.6)	
Systemic metastases*							0.01
Yes	26	(35.6)	16	(18.6)	7	(14.6)	
No	47	(64.4)	70	(81.4)	41	(85.4)	

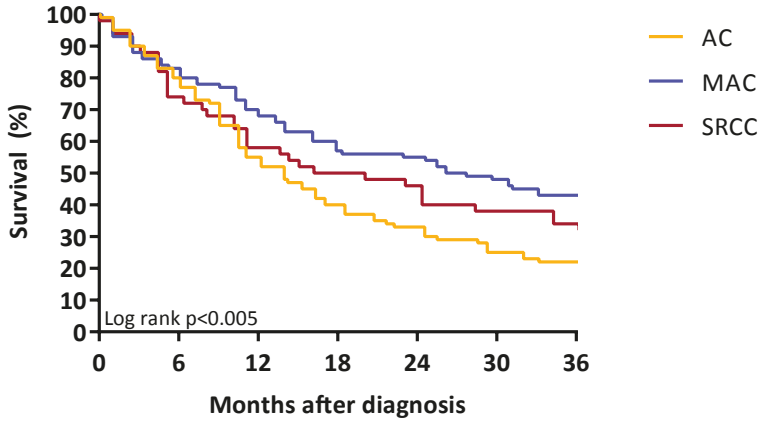
* Calculated for the patients with known metastatic sites only (n = 207)

Survival and prognostic factors

In locoregional disease, median overall survival was reached in none of the histologic subtypes, as more than 50% of the patients were alive at the end of the study period. The 5-year survival rates for patients with AC, MAC and SRCC were 60.0%, 60.5% and 69.6% respectively (p = 0.68). Histologic subtype was not a prognostic factor for overall survival. Multivariable survival analyses run for locoregional disease, showed that patients over 60 years old, compared to age <60 years had a lower overall survival (60-69 years vs <60 years; HR 1.91, 95% CI 1.24-2.94 and ≥70 years vs <60 years; HR 4.25, 95% CI 2.95-6.13). Crude 5-year survival rates were 80.9%, 67.1% and 43.4% for patients <60 years, 60-69 years and ≥70 years respectively.

In metastatic disease, median overall survival differed significantly among the histologic subtypes, being 12.6 months, 27.7 months and 18.1 months in metastatic AC, MAC and SRCC respectively ($p < 0.005$) (figure 2). One-year survival rates were 53.0%, 69.1% and 58.0% in AC, MAC and SRCC respectively. Multivariable survival analyses also revealed histologic subtype to be a relevant prognostic factor for overall survival in metastatic disease. Patients with metastatic MAC had a higher overall survival compared to those with AC (HR 0.48, 95%CI 0.34-0.69). The subtype SRCC was no prognostic factor compared to AC. In subanalyses, taking metastatic site into account, the histologic subtype MAC was only a positive prognostic factor compared to AC in patients with peritoneal metastases and not in other systemic metastases, as shown in table 3. Moreover, elderly over 70 years, compared to age <60 years (≥70 years vs <60 years; HR 1.99, 95%CI 1.38-2.88), had a lower overall survival, reflected in crude 5-year survival rates of 31.6% and 14.1% for patients aged <60 years and ≥70 years respectively.

Figure 2. Survival curve of patients with metastatic disease of appendiceal adenocarcinoma, mucinous adenocarcinoma and signet ring cell adenocarcinoma.



	Time to event (months)						
Patients at risk (n)	**0**	**6**	**12**	**18**	**24**	**30**	**36**
AC	83	65	44	32	26	20	18
MAC	97	79	67	55	53	46	42
SRCC	50	37	29	25	21	18	17

AC = adenocarcinoma, MAC = mucinous adenocarcinoma, SRCC = signet ring cell adenocarcinoma

Table 3. Median overall survival and multivariable survival analyses for patients with primary appendiceal adenocarcinoma according to extent of metastatic disease.

	N	Median overall survival (months)	Log rank *p*-value	HR*	(95% CI)
All metastases			< 0.005		
AC	83	12.6		1.00	(reference)
MAC	97	27.7		0.48	(0.34-0.69)
SRCC	50	18.1		0.89	(0.60-1.31)
Peritoneal metastases			< 0.0005		
AC	56	13.3		1.00	(reference)
MAC	83	31.2		0.42	(0.28-0.62)
SRCC	45	16.2		0.80	(0.52-1.23)
Systemic metastases			0.53		
AC	26	10.4		1.00	(reference)
MAC	16	10.7		1.07	(0.49-2.31)
SRCC	7	28.4		0.63	(0.24-1.63)

AC = (non-mucinous) adenocarcinoma, MAC = mucinous adenocarcinoma, SRCC = signet ring cell adenocarcinoma, HR = hazard ratio, CI = confidence interval, * adjusted for age, gender, period of diagnosis and treatment

Discussion

The current study evaluated the prognostic value of histologic subtype in patients with appendiceal adenocarcinomas in a verified population-based cohort. The histologic subtype, with special regard to mucinous histology, was shown to be only a favourable prognostic factor for overall survival in peritoneal metastatic disease, but not in locoregional disease or in systemic metastases.

In locoregional disease, the histologic subtype was not of prognostic relevance in overall survival. This finding is in line with the results of Widmann et al., which also showed no impact of histologic subtype in survival[5]. However, in metastatic disease, mucinous histologic subtype was a prognostic factor for higher overall survival, which was also observed in earlier research[1, 13]. Although it should be taken into consideration that the presence of peritoneal dissemination was the only factor of influence in metastatic disease, as patients with a mucinous tumour did not have a significant higher overall survival than patients with a non-mucinous tumour or SRCC in systemic metastases. These results are most likely a reflection of the biological behaviour of these tumours in peritoneal dissemination. MAC and SRCC both belong to the subgroup of mucinous appendiceal neoplasms, which are the principal cause of PMP[11, 14]. PMP is a rare clinical disease characterized by progressive accumulation of mucinous tumour deposition and mucinous ascites, which can be classified based on histologic features and its prognosis into four histologic subtypes, including acellular PMP, low-grade PMP, high-grade PMP and high-grade PMP with signet ring cells. MACs are the main cause of high-grade PMP, whereas SRCCs can give rise to high-grade PMP with signet ring cells[11, 14]. In contrast, non-mucinous tumours cause more frequently systemic metastases and classical non-mucinous peritoneal metastases, which harbour different clinical and prognostic features than PMP[11, 14].

In the different histologic subtypes, gender was not distributed equally among the subgroups in locoregional disease with a male predominance in SRCC. In metastatic disease, a significant female predominance was observed in all histologic subtypes. This observation is in contrast with colorectal cancer, where a male predominance is present in all disease stages[15, 16]. In mucinous peritoneal disease, it is known that the distinction between mucinous appendiceal neoplasms and ovarian cancer can be challenging, as mucinous appendiceal neoplasms can mimic ovarian mucinous tumors[17]. However, the observed relatively low percentage of ovarian metastases in all histologic subtypes in metastatic disease does not explain the female predominance.

Although the presented results were already adjusted for all available clinical prognostic factors, including treatment, the influence of the different applied treatment strategies

should be considered. Patients with peritoneal metastases may be treated with curative intent by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC). In patients with systemic metastases, currently only systemic palliative therapy is available. Moreover, patients with primary appendiceal mucinous tumours, including SRCC, are more likely to receive CRS+HIPEC in peritoneal dissemination than patients with a non-mucinous appendiceal tumour, probably because non-mucinous tumours more frequently simultaneously cause systemic metastases[18, 19]. However, the positive impact of CRS+HIPEC in patients with high-grade PMP with signet ring cells is not well determined[13, 20-22].

Strikingly, more than half of the patients initially diagnosed with a MAC were excluded from the present study. These tumours are now recognized as a LAMN or HAMN. Previously, these rare tumour types were not clearly defined, were unknown to some pathologists and could not be registered accurately in international cancer registries, due to one identical morphology code for PMP and mucinous adenocarcinomas. This finding underlines the urge of reassessment of pathologic reports of patients according to the newest consensus-based histopathological classification with a diagnosis or classification of an appendiceal MAC, as patients with a LAMN have a far better prognosis than patients with MAC, and may benefit from other treatment modalities[13, 14, 17].

Additionally, the population-based nature of the presented data is inherently associated with risks of several potential biases. In the NCR, data on numerous prognostic factors are not provided, including information on performance status, comorbidities, extent of the disease and disease related symptoms. Furthermore, only the primary treatment after diagnosis is registered, and therefore, data on for instance repeated CRS+HIPEC procedures are lacking. However, by creating a reliable study population through linkage of the NCR with PALGA, the present study could determine the true prognostic value of histologic subtype in patients with primary appendiceal adenocarcinomas.

In conclusion, mucinous histologic subtype is only a favourable prognostic factor compared to AC and SRCC in patients with peritoneal metastases of appendiceal adenocarcinoma, which might be a reflection of the biological behaviour of PMP compared to classic peritoneal metastases of non-mucinous origin. In locoregional disease and in systemic metastatic disease, histologic subtype has no prognostic impact in appendiceal adenocarcinoma. These results confirm that mucinous appendiceal adenocarcinomas, including SRCC, should be considered as a different entity, with respect to prognosis and possible treatment modalities.

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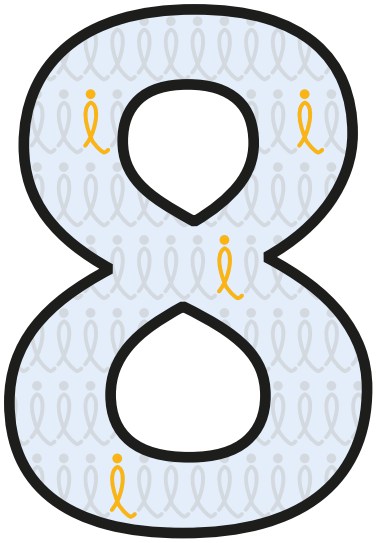

The clinical relevance of the histopathological classification for metastatic mucinous appendiceal neoplasms in a verified population-based cohort

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Abstract

Background: The study aimed to describe and evaluate the clinical disease course of primary metastatic mucinous appendiceal neoplasms, including low-grade appendiceal mucinous neoplasms (LAMNs), high-grade appendiceal mucinous neoplasms (HAMNs) and mucinous adenocarcinomas (MACs) in a population-based cohort.

Material and Methods: Data of patients with metastatic MACs diagnosed between 2001 and 2015, included in the Netherlands Cancer Registry (NCR) were used (n = 235). By linkage of the NCR with the Dutch Pathology Registry (PALGA), the histologic subtype was determined based on the latest histopathological classification for mucinous appendiceal neoplasms. Differences in patients and tumour characteristics and overall survival between the histological subgroups were described and evaluated.

Results: Of the 235 patients, 136 patients (57.8%) had a LAMN, 2 patients (0.9%) a HAMN and 97 patients (41.3%) a MAC. Female predominance was noted in both LAMN and MAC up to 77%. The peritoneal cavity was affected in 99% of the patients with metastatic LAMN, and in 97% of the patients with metastatic MAC. The 5-year survival rate was 78.4% in patients with metastatic LAMN, compared to 32.8% in metastatic MAC. In multivariable survival analyses, histologic subtype was of prognostic relevance (MAC vs. LAMN; HR 3.94, 95% CI 2.67-5.82).

Conclusion: In a verified population-based cohort, each subtype of mucinous appendiceal neoplasm has a distinct clinical disease course in metastatic setting. These results stress the importance to accurately diagnose patients with mucinous appendiceal lesions according to the latest proposed consensus-based histopathological classification.

Introduction

Mucinous appendiceal neoplasms are a subgroup of appendiceal epithelial tumours, which have been subdivided into a spectrum of mucinous lesions, including premalignant lesions, tumours of uncertain malignant potential and malignant lesions[1-6]. Tumours of uncertain malignant potential, consisting of low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs), have been of interest for several years, as these lesions are the leading cause of pseudomyxoma peritonei (PMP)[1, 2, 6, 7].

PMP is a clinical diagnosis characterized by the presence of excessive amounts of gel-like mucinous ascites in the peritoneal cavity, in contrast to the lack of mucin in non-mucinous peritoneal metastases[1, 4, 8, 9]. PMP is divided into low-grade PMP, formerly known as disseminated peritoneal adenomucinosis (DPAM), and high-grade PMP, previously called peritoneal mucinous carcinomatosis (PMCA)[2, 6-8, 10, 11]. Low-grade PMP is mainly caused by LAMNs, whereas high-grade PMP mostly originates from mucinous appendiceal adenocarcinomas[1, 2].

A global accepted classification for mucinous appendiceal neoplasms was lacking for multiple years, until the Peritoneal Surface Oncology Group International (PSOGI) recently introduced a consensus-based histopathological classification[1, 7]. Currently, the latest version of the WHO classification for mucinous appendiceal neoplasms is largely based on this PSOGI classification[12]. Due to the lack of a uniform classification in the past, historical research concerning LAMNs, HAMNs and mucinous adenocarcinomas (MACs) is likely to show inconsistencies or could even be invalid. Moreover, mucinous adenocarcinoma and PMP are classified with one corresponding morphology code, according to the International Classification of Diseases for Oncology (ICD-O), which could result in conflicting outcomes in studies on metastatic appendiceal cancer based on data from cancer registries[13]. The aim of the present study was to describe and evaluate the clinical disease course of metastatic mucinous appendiceal neoplasms, including LAMNs, HAMNs and MACs as classified according to the consensus-based histopathological classification of the PSOGI, in a verified population-based cohort.

Material and Methods

Data collection

Data from the Netherlands Cancer Registry (NCR) were used. The NCR collects population-based data on all newly diagnosed malignancies of all inhabitants of the Netherlands and covers an area of approximately 17 million citizens. Primary source of notification of the NCR is the automated nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses[14]. Information of patient and tumour characteristics, diagnosis and treatment are routinely extracted from the medical records by specially trained registrars of the NCR. Primary tumours are staged according to the Tumour Node Metastasis (TNM) classification. In case of missing pathological data, the clinical TNM stage is used. The topographical site of the primary tumour and systemic metastases are registered according to the third version of the ICD-O. Unfortunately, the exact topographical metastatic site was not collected until 2008 in some regions of the NCR. Vital status of patients is collected through linkage of the NCR with civil municipal registries and the central bureau for genealogy, which collects data on all deceased Dutch inhabitants. Follow-up was complete until 31 January 2019.

Study population

All consecutive patients diagnosed with primary mucinous appendiceal adenocarcinomas (ICD-O code C18.1, morphology codes 8470, 8480 and 8481) with synchronous metastatic disease ($T_{1-4}N_{0-2}M_1$) between 2001 and 2015 were included in this study. Patients with non-mucinous and signet ring cell appendiceal adenocarcinomas were excluded.

As multiple tumour classifications of appendiceal mucinous neoplasms were used interchangeably over time, and mucinous adenocarcinomas and PMP were classified with one corresponding morphology code, the group of patients who was classified with mucinous appendiceal adenocarcinomas could be inappropriate in the NCR. In order to establish the actual histologic subtype of appendiceal mucinous neoplasms, pathological reports, including macroscopy and microscopy reports, of patients with appendiceal mucinous adenocarcinomas in metastatic disease with morphology codes 8470 and 8480, in which formerly classified cystadenomas (8470/0) and presently LAMNs (8480/1), HAMNs or PMP (8480/6) could be included, were linked with PALGA (n = 235) and retrospectively revised for the patients concerned. Patients with morphology code 8481 were not linked, due to its impossibility to classify PMP or low-grade lesions. The first assessment of the pathological reports was performed by LL, and afterwards checked and revised by CH, a pathologist with special interest in mucinous appendiceal neoplasms.

The histologic subtype was retrospectively adjusted for the patients concerned, according to the most recent histopathological classification for mucinous appendiceal neoplasms[1]. If a HAMN, low-grade PMP of a mucinous adenocarcinoma or high-grade PMP of a LAMN was suspected, based on the pathological reports, the original tissue sections were requested from the hospital of initial diagnosis or hospital of treatment. Pathologist CH reviewed the tissue sections, after which a decisive diagnosis on histologic type of the primary lesion, and if necessary of the peritoneal grade in case of discordant histology, was made, based on the last PSOGI classification.

Statistical analysis

The patient and tumour characteristics of the study population were first described. Differences in patient and tumour characteristics between the histologic subgroups were analysed with a two-sided chi-square test or a fisher's exact test as appropriate. Survival was computed on all-cause mortality, and was defined as the time from date of diagnosis to date of death or last follow-up date for patients who were lost to follow-up or emigrated. Patients who were still alive at 1 February 2019 were censored. Survival was subsequently calculated with the log-rank test and Kaplan-Meier analyses. The cox proportional hazards model was run to identify prognostic factors for overall survival. In the analyses, an adjustment for treatment was made, in which different kind of treatment strategies were taken into account, including surgery for both the primary tumour and metastatic sites, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC), systemic therapy (chemotherapy + targeted therapy) and radiotherapy. Hazard ratios (HRs) were presented with 95% confidence intervals (CIs).

For all analyses, the statistical package SAS Statistical Software (version 9.4, SAS Institute, Cary, NC, USA) was used. A two-sided p-value of $p < 0.05$ was considered as statistically significant for all statistical tests.

Results

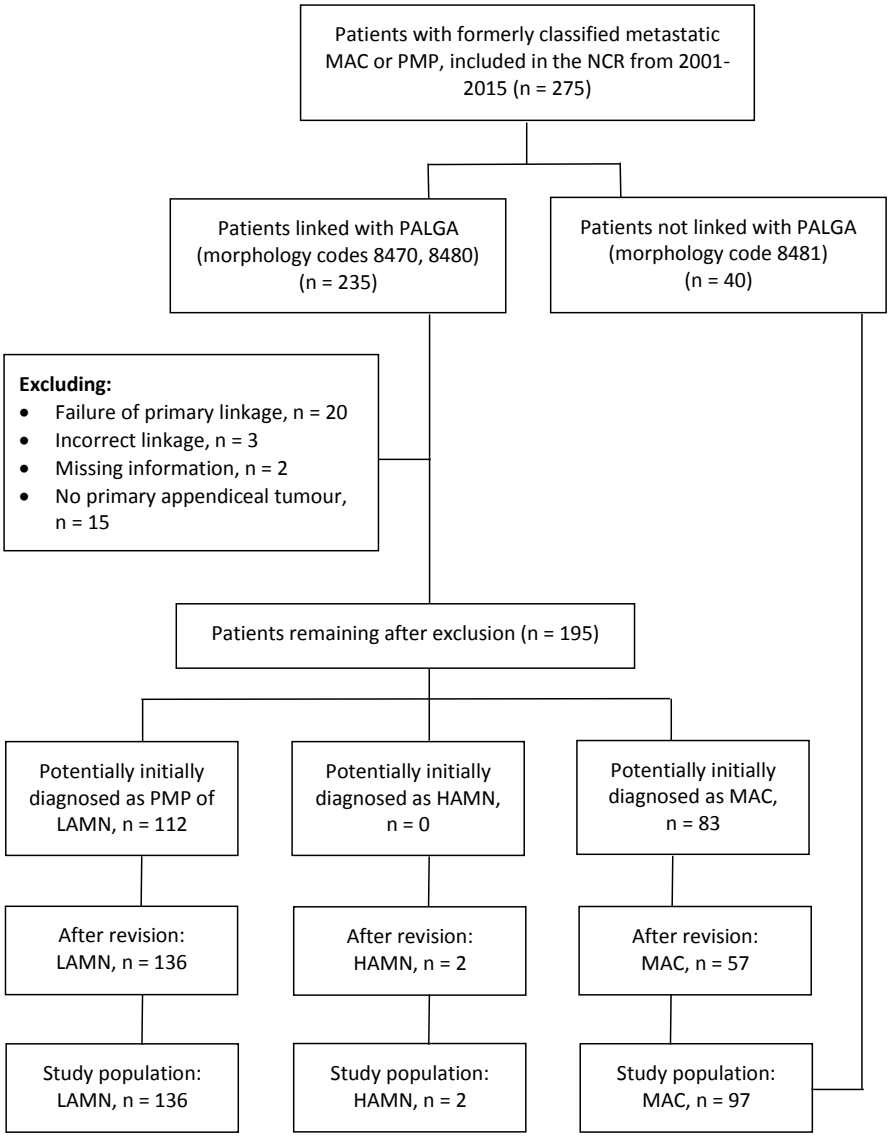
A total of 275 patients with metastatic MAC diagnosed between 2001-2015 was initially included in the study, of whom 235 were linked with PALGA for reassessment. After reassessment of the pathologic reports, 40 patients were excluded for several reasons, including failure of primary linkage, missing information or having a non-primary appendiceal origin. After merging these patients with the 40 patients for whom pathologic reassessment was not performed, 235 patients remained in the formerly classified group of metastatic mucinous appendiceal adenocarcinoma or PMP. These 235 patients were categorised in one of three subgroups: 136 patients were diagnosed with a LAMN, 2 with a HAMN and 97 patients with a MAC (figure 1).

As the subgroup of patients with a HAMN only consisted of 2 patients, no reliable statements can be drawn from statistical analyses when comparing with LAMNs and MACs, and therefore, patients with LAMNs and MACs were analysed statistically and the patients with a HAMN were described.

In both patients with LAMN and MAC, a significant female predominance was observed (~75%). Median age of patients with a primary LAMN was 61 years and 63 years in MAC. Although not statistically significant, the absolute number of patients diagnosed with metastatic LAMN and MAC increased over time (table 1).

For patients with known metastatic sites (n = 211, 90.6%), peritoneal dissemination was present in 99% of the patients with LAMN and 97% of the patients with MAC. In the only patient with LAMN without peritoneal dissemination, the pleura was affected. One patient with a primary LAMN had a regional pathologic confirmed lymph node metastasis. In three patients with a primary MAC, there were liver and/or lung metastases without signs of peritoneal metastases. Both patients with metastatic HAMN had low-grade peritoneal dissemination. Of the patients with suspected discordant histology of the primary and metastatic lesions, pathologic assessment showed no discordances with only low-grade PMP of LAMN and high-grade PMP of MAC.

Figure 1. An overview of the included patients with metastatic mucinous appendiceal neoplasm, diagnosed between 2001 and 2015 in the Netherlands.



MAC = mucinous adenocarcinoma, PMP = pseudomyxoma peritonei, LAMN = low-grade appendiceal mucinous neoplasm, HAMN = high-grade appendiceal mucinous neoplasm, PALGA = Dutch Pathology Registry

Table 1. General characteristics of patients with a metastatic mucinous appendiceal neoplasm, diagnosed between 2001 and 2015 in the Netherlands.

	LAMN (n = 136)		**HAMN** (n = 2)		**MAC** (n = 97)		
	N	(%)	N	(%)	N	(%)	*p*-value*
Gender							0.73
Male	31	(22.8)	2	(100.0)	24	(24.7)	
Female	105	(77.2)	0	(0.0)	73	(75.3)	
Age (years)							0.72
< 60	61	(44.9)	1	(50.0)	42	(43.3)	
60-69	42	(30.9)	0	(0.0)	27	(27.8)	
≥ 70	33	(24.3)	1	(50.0)	28	(28.9)	
Period							0.32
2001-2005	29	(21.3)	1	(50.0)	24	(24.7)	
2006-2010	43	(31.6)	0	(0.0)	37	(38.1)	
2011-2015	64	(47.1)	1	(50.0)	36	(37.1)	
Peritoneal involvement (including ovarian)**							0.16
Yes	122	(99.2)	2	(100.0)	83	(96.6)	
No	1	(0.8)	0	(0.0)	3	(3.4)	
Ovarian involvement**							0.50
Yes	50	(40.7)	0	(0.0)	31	(36.1)	
No	73	(59.4)	2	(100.0)	55	(64.0)	

* calculated between LAMN and mucinous adenocarcinoma.
** shown for the patients with known metastatic sites (n = 211), as <2008 the topographic code for metastases were not reported in all regions of the NCR.
LAMN = low-grade appendiceal mucinous neoplasm, HAMN = high-grade appendiceal mucinous neoplasm, MAC = mucinous adenocarcinoma

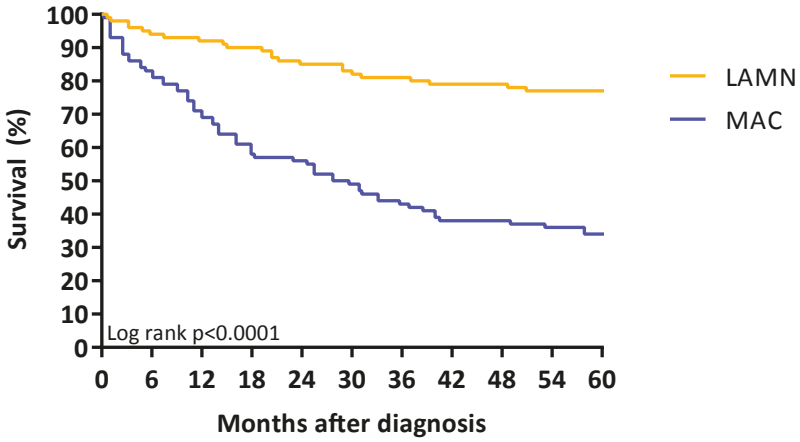
In the group of treated patients, surgical resection of the primary tumour and/or the metastatic sites, was performed in 100% of the patients with metastatic LAMN, compared to 93.3% of the patients with metastatic MAC ($p < 0.005$). CRS+HIPEC was performed in 69.8% of the patients with a peritoneal disseminated LAMN at initial presentation, compared to 45.5% of the patients with peritoneal metastases of MAC ($p < 0.001$). Palliative systemic therapy was administered to 14.4% of the patients with metastatic LAMN, whereas in metastatic MAC 50.6% of the patients was treated with systemic therapy. In 20 of these 45 patients with metastatic MAC receiving palliative systemic therapy, initial CRS+HIPEC was also performed.

Overall survival was calculated per histologic subtype (figure 2). The 5-year survival rate accounted 78.4% in LAMN and 32.8% in MAC. Median overall survival could not be calculated in metastatic LAMN as less than 1 in 3 patients were deceased at last follow-up date. Median overall survival was 27.7 (95% CI 16.1-40.0) months in metastatic MAC. In the subset of

patients with a metastatic MAC receiving CRS+HIPEC and/or palliative chemotherapy, the median overall survival was 72.2 (40.5-81.6) and 31.8 (14.8-49.0) months respectively. The two patients with metastatic HAMN had an overall survival of 13.9 and 127.0 months respectively.

In multivariable survival analyses, histologic subtype was of prognostic relevance (MAC vs. LAMN; HR 3.94, 95% CI 2.67-5.82), as shown in table 2.

Figure 2. Overall survival of patients with metastatic disease of low-grade appendiceal mucinous neoplasm (LAMN) and appendiceal mucinous adenocarcinoma (MAC).



	Time to event (months)										
Patients at risk (n)	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
LAMN	136	128	126	122	117	114	111	100	98	89	84
MAC	97	79	67	55	53	46	42	37	36	31	30

LAMN = low-grade appendiceal mucinous neoplasm, MAC = mucinous adenocarcinoma

Table 2. The cox proportional hazards model for patients with metastatic disease of a low-grade appendiceal mucinous neoplasm (LAMN) and mucinous appendiceal adenocarcinoma (MAC).

n = 233	HR*	(95% CI)
Gender		
Male	1.00	(reference)
Female	0.72	(0.47-1.09)
Age (years)		
< 60	1.00	(reference)
60-69	1.68	(1.07-2.65)
≥ 70	1.90	(1.23-2.97)
Period		
2001-2005	1.00	(reference)
2006-2010	0.63	(0.40-0.99)
2011-2015	0.79	(0.49-1.25)
Morphology		
LAMN	1.00	(reference)
MAC	3.94	(2.67-5.82)

* Adjusted for all factors listed, including treatment (not shown).
HR = hazard ratio, CI = confidence interval

Discussion

This study described the distinct disease course of patients with LAMNs, HAMNs and mucinous appendiceal adenocarcinomas after reassessment of pathological reports based on the recent PSOGI guideline, in a subset of patients which was formerly classified as metastatic MAC or PMP. It was shown that each subtype of metastatic mucinous appendiceal neoplasm has a distinct clinical disease course, as observed in the 5-year survival rates of 78.4% in metastatic LAMN and 32.8% in metastatic MAC.

The observed overall survival rates in patients with confirmed metastatic disease of LAMNs and MACs after pathologic reassessment, demonstrated the large differences in clinical disease course between metastatic disease originating from LAMNs and MACs. The 5-year survival rate was more than twice as high in patients with metastatic LAMN compared to patients with metastatic MAC. As nearly all patients in both histologic subtypes had peritoneal dissemination, the survival rates are largely a reflection of the differences between low-grade and high-grade PMP.

In comparison to previous studies, the observed survival rates for metastatic LAMN are in line with the 5-year overall survival rates of patients with DPAM and treated with CRS+HIPEC in other studies[15-17]. If compared to a recent study, the observed overall survival of patients with metastatic LAMN was slightly higher[18]. In metastatic MAC, the overall survival of patients in the current study was significantly lower as compared to the survival of patients with PMCA in previous studies. However, in these previous studies, the patients with PMCA were all treated with CRS+HIPEC and/or systemic therapy, whereas in the present study only 45% of the patients with metastatic MAC were primary treated with CRS+HIPEC[15-17, 19-21]. For the patients with MAC in the current study treated with CRS+HIPEC and/or systemic therapy, the observed overall survival is in line with the published literature[15-17, 19-21].

In the current study, initial CRS+HIPEC was performed in two-thirds of the patients with metastatic LAMN, which was significantly higher than in patients with metastatic MAC. CRS+HIPEC is the recommended treatment of choice for patients with all types of PMP, especially in patients with low-grade PMP of LAMN[8, 15-17]. In these patients, the use of CRS+HIPEC is considered as a curative treatment option, irrespective of the peritoneal tumour burden[2, 16, 22]. However, in high-grade PMP, the beneficial effect of CRS+HIPEC is generally limited to the subgroup of patients with a low peritoneal tumour load. Prior research has demonstrated that a high peritoneal tumour burden, reflected in peritoneal cancer index (PCI) score ≥ 20, is associated with a significant poorer survival in high-grade PMP, even after CRS+HIPEC[2, 23]. Probably, the use of CRS+HIPEC in both subgroups in daily practice was higher and underestimated in the present study due to several reasons. Firstly, only data

on the initial treatment is available in the NCR. Consequently, data on repeated CRS+HIPEC procedures, which is known to occur frequently in patients with PMP to increase overall survival, are not recorded. Secondly, in one of the tertiary hospitals in the Netherlands who perform CRS+HIPEC, data on CRS+HIPEC were not routinely noted until 2011.

The presented results showed that the absolute number of patients diagnosed with metastatic LAMN and MAC increased over time, most likely caused by the decreasing misclassification of LAMNs as gynaecological mucinous tumours and the increased awareness of mucinous appendiceal neoplasms in daily practice[1, 9]. Moreover, it should be taken into consideration that several patients were excluded based on the pathological reports, mainly in the earliest study period. For instance, some patients were excluded due to missing information or unclear pathological reports, including conclusions as 'very well differentiated mucinous appendiceal adenocarcinoma'.

An exceptional female predominance of approximately 75% was noted in both patients with LAMN and MAC. This percentage is higher compared to a previous study, where approximately 60% of the patients with LAMN were female, for which a substantiated explanation is lacking[18]. Notably, female BRCA1/2 mutation carriers have an over 1000-fold increased risk for intraperitoneal cancer, including PMP originating from a LAMN, with a lifetime risk of approximately 12% in patients with a BRCA1-mutation, even after risk-reducing or prophylactic salpingo-oophorectomy[24]. However, the prevalence of BRCA1/2 mutation carriers in the general population is too low to explain the high female predominance as found in the current study.

For the present study, only patients with metastatic disease were included to create a homogenous group of patients, since a primary LAMN without peritoneal spread is considered as a benign lesion, and therefore, these patients are generally not collected in international cancer registries[2, 18, 25]. It could be assumed that the overall survival of patients with a locoregional LAMN included in the NCR is an underestimation of the overall survival of the total group of patients with locoregional LAMN, due to the initial overdiagnosis of these patients as having a MAC.

Unfortunately, several limitations of the current study are inherent to its population-based nature. Data on several prognostic factors are lacking, including clinical performance status, comorbidities, extent of the peritoneal disease, disease related symptoms, the serum levels of the tumour markers CEA, CA19-9 and CA-125 and the mutational status of the primary tumour such as RAS or BRAF. Moreover, only data on the primary treatment is registered in the NCR. Therefore, repeated treatment procedures and data on for instance palliative

systemic therapy after an initial curative CRS+HIPEC are lacking.

In conclusion, it is shown that patients in a population-based setting with metastatic disease of LAMN and MAC have a distinct clinical disease course, reflected in 5-year survival difference of over 40% in the advantage of patients with metastatic LAMN. These results show the importance to diagnose patients with mucinous appendiceal lesions correctly and according to the latest proposed consensus-based histopathological classification.

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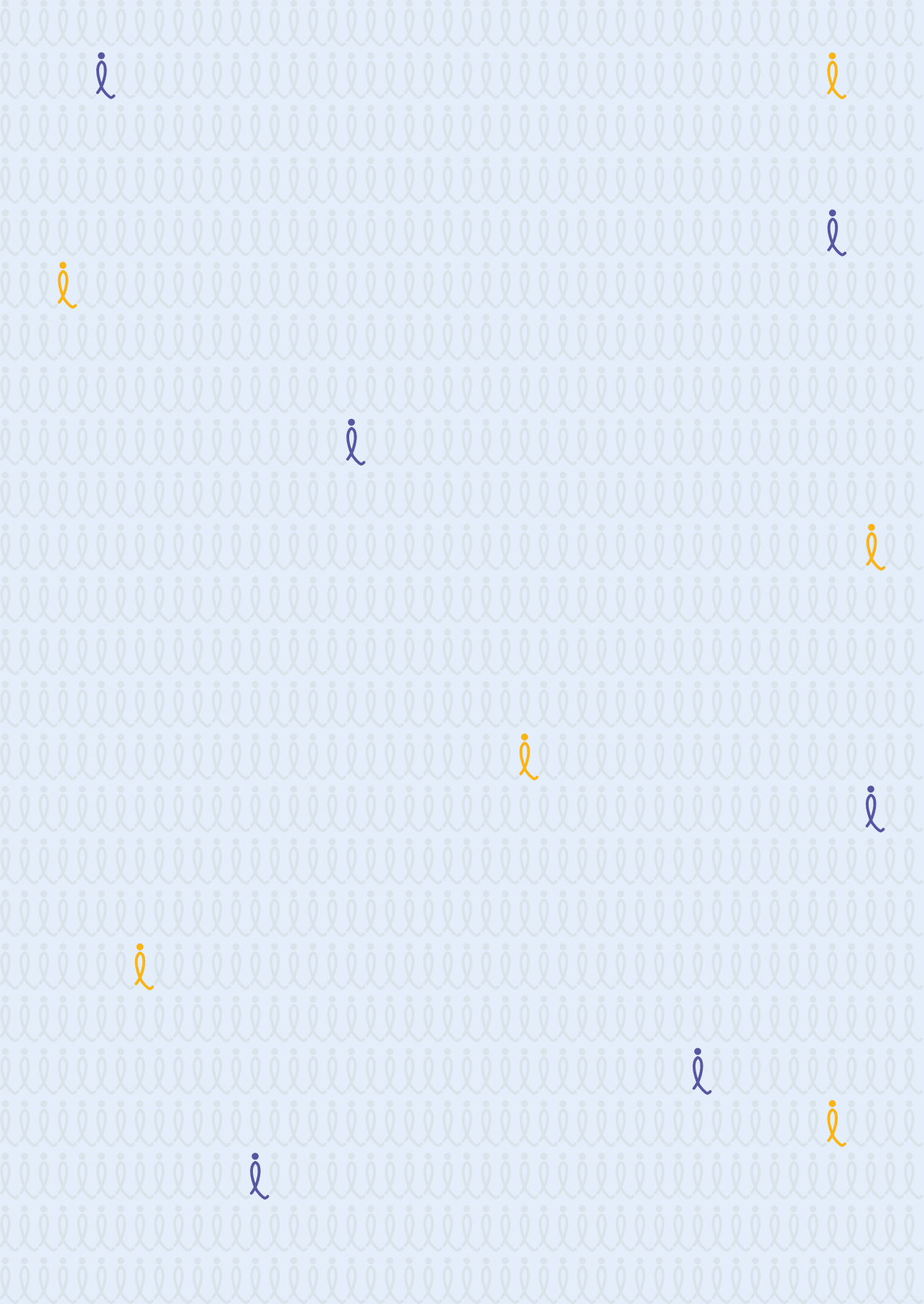

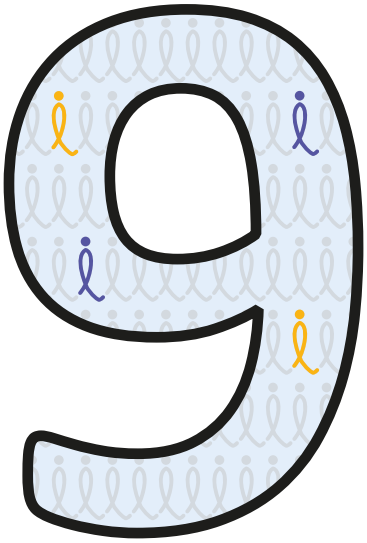

Summary and general discussion

In this final chapter, the main findings of the studies performed in this thesis are summarized and subsequently discussed in a broader context. Afterwards, several methodological considerations are discussed that should be taken into account when interpreting the results of the studies presented in this thesis. Also implications for clinical practice and future research are discussed.

Summary of the main findings

This thesis aimed to provide insight into clinical and pathological aspects of small bowel and appendiceal cancer, by examining the epidemiology, clinical disease course, treatment and prognostic factors of these rare gastrointestinal cancers.

In **part I** of this thesis, insight into the epidemiology of small bowel cancer was provided, by studying the incidence, trends in treatment and overall survival. In **chapter 2**, the incidence, treatment and overall survival over time of patients with small bowel adenocarcinoma (SBA) in both locoregional and metastatic disease was established by conducting one of the largest population-based studies in SBAs to date. The study revealed an increasing incidence of SBAs, which was mainly caused by an absolute twofold increase of duodenal tumours in the latest years, from 233 patients in the study period 1999-2003 to 478 patients in 2009-2013. Moreover, the percentage of patients presenting with synchronous metastases increased over time as well, from 27% in 1999-2003 to almost 40% of the patients a decade later. The most common metastatic sites were the liver (46%) and the peritoneal cavity (29%), although differences in metastatic pattern were recognizable between the primary tumour locations. Patients with a primary duodenal tumour more frequently presented with liver metastases (54%), whereas patients with a more distal tumour more often had peritoneal metastases (44%). In locoregional disease, the prescription of adjuvant chemotherapy was associated with higher survival rates. In metastatic disease, the administration of palliative chemotherapy increased over time, but median overall survival remained stable around 4-5 months.

The incidence, risk factors and treatment-related survival of patients with peritoneal metastases of SBA, one of the most frequent encountered metastatic sites, was studied in **chapter 3**. Synchronous peritoneal metastases were found in 13% of all patients with SBA, of which the incidence increased over time, especially in patients with a non-duodenal tumour (22% of the patients in 2010-2014). In comparison to all patients with a SBA, patients with peritoneal metastases were younger, more often had a primary non-duodenal tumour and more often had an advanced T- and N-stage. Median survival with supportive care only was very poor, and was found to be only 2.5 months. Patients treated with palliative chemotherapy, surgery of the primary tumour or cytoreductive surgery with hyperthermic

intraperitoneal chemotherapy (CRS+HIPEC) showed a median overall survival of 11, 11 and 32 months respectively.

Part II of this thesis evaluated the use and effects of palliative systemic treatment in patients with metastatic small bowel cancer. As details on systemic treatment are not routinely collected in the Netherlands Cancer Registry, additional data on first-, second- and third-line systemic treatment regimens, including details and duration of the chemotherapeutical and targeted agents, of patients diagnosed with metastatic SBA between 2007 and 2016 were nationwide retrospectively assembled in March of 2018. **Chapter 4** addressed the use and effects of palliative chemotherapy. Palliative chemotherapy was received by 199 patients (38%) with metastatic disease. Patients who received palliative chemotherapy were younger than non-treated patients (63 vs. 72 years). The first-line chemotherapy regimens were mainly based on fluoropyrimidines (5-fluorouracil and capecitabine) and oxaliplatin. First-line combination chemotherapy was prescribed to 80% of the patients, of which 97% received an oxaliplatin-based doublet or triplet regimen, including capecitabine (CAPOX), 5-fluorouracil (FOLFOX) or epirubicin with capecitabine (EOX). Single-agent chemotherapy in first-line treatment mostly consisted of capecitabine (86%). Multivariable logistic regression showed that elderly patients (≥70 years) had a lower chance to receive first-line combination chemotherapy and second-line treatment as well (65% and 12%, respectively). Second-line systemic therapy was received by only 27% of the patients, mostly consisting of single-agent chemotherapy (58%) with a preference for irinotecan. Third-line systemic therapy was administered in only 6% of the patients. The median overall survival for patients treated with palliative chemotherapy was 9.3 months, compared to 3.0 months for patients only receiving best supportive care. After first-line therapy only, median overall survival of patients receiving single-agent chemotherapy was 5.6 months, compared to 7.0 months with combination chemotherapy.

In **chapter 5**, insight into the use and effectiveness of the addition of targeted therapy to palliative chemotherapy in patients with synchronous metastases of SBA was provided. It was shown that only 25 patients (13%) received additional targeted therapy in first-line treatment, exclusively bevacizumab. In almost all cases (96%), bevacizumab was added to combination chemotherapy with CAPOX or FOLFOX. Patients with a primary ileal tumour were more likely to receive bevacizumab than patients with more proximal tumours. Median overall survival was 9.3 months for patients treated with chemotherapy and additional bevacizumab, and 9.1 months for patients treated with chemotherapy only. For comparing survival outcomes of patients treated with and without additional targeted therapy in first-line treatment, a propensity score matched sample was generated to eliminate potential endogeneity bias. In the group of patients in whom bevacizumab was added to first-line

chemotherapy, the median overall survival was 8.5 months, compared to 6.4 months in patients exclusively treated with first-line chemotherapy, with equal 1-year survival rates of 25%. In multivariable regression analyses, the use of first-line bevacizumab was no prognostic factor (HR 1.25, 95% CI 0.70-2.24). Also in the propensity score matched sample, the additional use of first-line bevacizumab was no prognostic factor for survival (HR 1.09, 95% CI 0.53-2.26).

In **part III** of this thesis, the prognostic value of histologic subtype in appendiceal cancer was studied, with special attention to mucinous appendiceal neoplasms. In the past years, new insights were gathered with regard to mucinous appendiceal neoplasms and its relation to pseudomyxoma peritonei (PMP). More specifically, clear and universal definitions for mucinous appendiceal neoplasms were established by the development of an international consensus-based histopathological classification regarding mucinous appendiceal neoplasms. In **chapter 6** an overview of the basic terminology of the histologic subtypes in mucinous appendiceal neoplasms was provided, with tentative recommendations for the management of these neoplasms for clinicians encountering patients with these diseases. Mucinous appendiceal neoplasms can be distinguished into 3 subgroups, including true premalignant lesions or adenomas, tumours of uncertain malignant potential, known as low-grade mucinous appendiceal neoplasms (LAMNs) and high-grade mucinous appendiceal neoplasms (HAMNs), and malignant lesions, including mucinous and signet ring cell adenocarcinomas. PMP is the clinical term for peritoneal disease of mucinous appendiceal neoplasms. It is distinguished from usual non-mucinous peritoneal metastases by the presence of excessive amounts of mucin in the peritoneal cavity. Analogous to the primary lesions, PMP is subdivided into several categories, based on histologic subtype, including acellular PMP, low-grade PMP, high-grade PMP and high-grade PMP with signet ring cells. Potential treatment options for the primary lesions, as well as for the peritoneal disease of mucinous appendiceal neoplasms were summarized. In locoregional disease, surgical resection should be performed. In PMP, CRS+HIPEC should be considered for all types of PMP, taking the potential benefits and harms for the patients with the specific subtype into account. Palliative chemotherapy can be considered in patients with high-grade PMP and high-grade PMP with signet ring cells, but not in the other two subcategories. The role of targeted therapy should be better determined.

For **chapter 7 & 8** of this thesis, additional data of the Dutch Pathology Registry (PALGA) was linked with the NCR to create a uniform group of patients with mucinous appendiceal neoplasms, according to the newest histopathological classification. In **chapter 7** of this thesis, the true prognostic value of histologic subtype, with use of this new consensus-based histopathological classification, in a subset of patients with mucinous, non-mucinous and

signet ring cell adenocarcinomas was determined. The study showed that in locoregional disease, histologic subtype was not a prognostic factor for overall survival, with 5-year survival rates for patients with non-mucinous adenocarcinoma, mucinous adenocarcinoma and signet ring cell adenocarcinoma of 60.0%, 60.5% and 69.6% respectively. However, in metastatic disease, mucinous adenocarcinoma was associated with higher survival compared to non-mucinous adenocarcinoma (median overall survival 27.7 vs. 12.6 months, HR 0.48, 95%CI 0.34-0.69). Signet ring cell adenocarcinoma was no prognostic factor compared to non-mucinous or mucinous histology. In sub analyses, taking metastatic site into account, mucinous histology was only a positive prognostic factor compared to non-mucinous histology in peritoneal metastases (median overall survival 31.2 vs. 13.3 months, HR 0.42, 95%CI 0.28-0.62) and not in systemic metastases (median overall survival 10.7 vs. 10.4 months, HR 1.07, 95%CI 0.49-2.31).

Chapter 8 described and evaluated the clinical disease course of metastatic mucinous appendiceal neoplasms, including LAMNs, HAMNs and mucinous adenocarcinomas as classified according to the latest consensus-based histopathological classification, in a verified population-based cohort. It was shown that of the 235 patients registered as metastatic mucinous appendiceal adenocarcinoma or PMP, 136 patients (57.9%) had a LAMN, 2 patients (0.9%) a HAMN and 97 patients (41.1%) a mucinous appendiceal adenocarcinoma after pathological reassessment of pathologic reports and in some cases of tissue sections. Survival rates were dependent on histologic subtype, as the 5-year survival rate amounted to 78.9% in patients with metastatic LAMN, compared to 33.2% in metastatic mucinous adenocarcinoma. Also multivariable survival analyses revealed histologic subtype to be of prognostic relevance in metastatic disease (mucinous adenocarcinoma vs. LAMN; HR 3.90, 95%CI 2.64-5.76).

General discussion

Due to the rarity of small bowel and appendiceal cancer, it is difficult to conduct prospective cohort studies or randomized controlled trials. However, clinicians are confronted with patients with these diseases in clinical practice. Therefore, this thesis aimed to obtain insights into the clinical and pathological aspects of these two rare gastrointestinal cancers.

Increasing incidence in small bowel and appendiceal cancer

The absolute number of patients newly diagnosed with small bowel and appendiceal cancer has increased over the years, which is mainly caused by the improvement of imaging and endoscopical techniques. In particular, with the ongoing development of the quality of cross-sectional imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), tumours in both the small bowel and appendix could be detected more easily, at an earlier stage and more frequently preoperatively[1-3]. In small bowel cancer, especially the development of CT and magnetic resonance (MR) enterography improved the detection of the neoplastic lesions. In studies comparing these techniques with tissue and endoscopic findings, an accuracy of 97% was found in MR enterography[4-6]. Other new diagnostic tools to enhance preoperative exploration of the small bowel include video capsule endoscopy (VCE) and double-balloon enteroscopy (DBE), in which small bowel abnormalities could be detected in the majority of cases[7]. This enhanced detection could also partly explain the increased incidence of SBA in the study presented in this thesis.

As presented in this thesis, the increasing incidence rates in SBAs were mainly accountable to the significant twofold rise of duodenal adenocarcinomas. The increase in duodenal adenocarcinomas was also observed in other population-based studies, with even an six fold increase in both sexes in Sweden in the period 1960-2009[8-11]. Several hypotheses have been formulated for the differing cancer incidence rates in the duodenum and the more distal small bowel. First, the improved quality of imaging techniques could have caused a decline in misclassification of duodenal adenocarcinomas as pancreatic cancer or adenocarcinoma of unknown primary in metastatic disease[10, 12]. Secondly, lifestyle associated risk factors could play a role as well, as it is known that a high sugar and refined carbohydrate intake predisposes for small bowel cancer. Since the duodenum is the first part of the gastrointestinal tract responsible for the absorption of nutritional elements, ingested carcinogens reach the highest concentration in the duodenum[6, 10, 13].

The improved diagnostic accuracy may have led to an increase in the proportion of patients diagnosed with metastatic disease as well[3, 4]. In the present thesis, the proportion of patients diagnosed with synchronous metastatic disease increased from 27% in 1999-2003 to even 38% of the patients in 2009-2013. The proportion of patients diagnosed with peritoneal

dissemination also increased over time, especially in patients with a primary jejunal and ileal tumour, in which 22% of the patients was found to have peritoneal metastases in the period 2010-2014. It is thought that peritoneal metastases of a primary duodenal tumour are less common due to its retroperitoneal location, which makes direct contiguous tumour spread to the peritoneal cavity less likely[14, 15].

Palliative systemic therapy in metastatic small bowel cancer

Although metastatic disease is frequently encountered in SBA, limited data exists on the role of palliative systemic therapy. Moreover, no standard frontline regimen has been defined due to the lack of randomized trials[16-18]. In this thesis, only 38% of the patients with metastatic disease was treated with palliative systemic therapy, even in the most recent years. The percentage of treated patients is low, compared to colorectal cancer[19, 20].

As several molecular alterations between small bowel cancer and both gastric and colorectal cancer overlap, patients with metastatic SBA are often treated with the same systemic regimens as patients with metastatic gastric or colorectal cancers[16-18, 21]. These regimens have been studied in a subset of retrospective and phase II studies, and mainly include the cytotoxic agents 5-fluorouracil, capecitabine, oxaliplatin and cisplatin[16-18, 22-29].

Early retrospective studies reported on patients treated with the single-agent 5-fluorouracil, showed low response rates ranging from 7% to 36%[30, 31]. The Eastern Cooperative Oncology Group (ECOG) performed between 1983 and 1985 a phase II study with the FAM regimen, a combination of 5-flourouracil, doxorubicin and mitomycin C, as this regimen had shown promising results in gastric cancer. However, the response rate of the treated patients with metastatic SBA was only 18%[23]. Subsequently conducted research mainly studied the combination of a fluoropyrimidine and a platinum compound, as cisplatin and oxaliplatin. In 2008, a retrospective study by Overman et al. showed that 5-flourouracil and a platinum agent significantly improved response rates from 16% to 46% and progression-free survival from 3.9 months to 8.7 months, in a subset of 80 patients, compared to all other used systemic regimens[16]. In 2010, Zaanan et al. revealed a superiority of oxaliplatin-based combination chemotherapy over cisplatin-based therapy in terms of both progression free survival (6.9 vs 4.8 months, $p \leq 0.0001$) and overall survival (17.8 vs 9.3 months, $p = 0.02$)[18]. Additional small phase II studies using doublet oxaliplatin-containing palliative chemotherapy regimens showed promising results with response rates around 50% and a median overall survival of approximately 15 to 17 months[24, 26, 28]. As phase II trials are associated with several major limitations, the implications of these kind of studies for daily clinical practice are often limited. In the present thesis, it was shown that in daily practice only a minority of the patients with metastatic SBA was treated with palliative

chemotherapy. This thesis confirmed the use of oxaliplatin-based chemotherapy in first-line treatment, which also impacted the median overall survival on a population-based level, suggesting CAPOX/FOLFOX could be a reasonable option for first-line treatment in patients with metastatic SBA in clinical practice.

In the subset of patients with peritoneal metastases, it was shown in this thesis that the use of palliative chemotherapy in peritoneal metastases of SBA resulted in a population-based improvement of median overall survival, which contrast the general opinion of peritoneal metastases as a virtually untreatable disease[15]. For these patients, the suggested frontline regimen could also serve as a potential treatment option.

In addition to palliative chemotherapy, the role of several targeted agents in SBA has been studied, as several molecular alterations in SBA could serve as a potential target for targeted therapy in clinical care[6, 21, 32, 33]. Genomic profiling of patients with SBA has shown a high expression of vascular endothelial growth factor-A (VEGF-A) in 92% of the patients, suggesting a potential role for the targeted agent bevacizumab[6, 34]. However, it should be taken into account that in metastatic disease a higher percentage of patients has a lower VEGF-A expression[34]. Only one phase-II study addressed the benefit of additional bevacizumab to palliative combination chemotherapy with CAPOX, which showed no significant differences in progression-free or overall survival compared to combination chemotherapy with CAPOX only[35]. Moreover a retrospective study by Aydin et al. also showed no statistically significant improvement in progression-free or overall survival with the addition of bevacizumab to palliative chemotherapy, compared to combination chemotherapy with FOLFOX or FOLFIRI only[36]. In daily practice, this thesis showed that only 13% of the patients received additional bevacizumab to palliative chemotherapy, which resulted in equal median overall survival and one-year survival rates compared to patients treated with palliative chemotherapy only. All these results might indicate a limited clinical effect of bevacizumab in addition to palliative chemotherapy in daily practice on overall survival. However, as 91% of the SBAs harboured a potentially targetable genomic alteration, the role of other targeted agents should be further investigated[21]. The high incidence up to 35% of microsatellite instability (MSI) in SBA could suggest a potential role for checkpoint immunotherapy[6, 21, 34, 37, 38].

Prognostic value of histologic subtype in appendiceal cancer

Historically, appendiceal cancer was classified according to colorectal cancer up to the 6th edition of the TNM (TNM-6) classification of malignant tumours[39]. In the past years, several new insights were gathered in appendiceal cancer, including neuroendocrine tumours, goblet cell tumours, mucinous appendiceal neoplasms and carcinomas[40-43]. As a result of these advancing insights, appendiceal cancer and colorectal cancer were classified

separately since the establishment of the TNM-7 in 2010[44].

Mucinous histologic subtype is thought to be of prognostic relevance in patients with mucinous appendiceal neoplasms and adenocarcinomas[45-48]. However, a lot of research was conducted in the time period before the development of the recent consensus-based histopathological classification for mucinous neoplasms, including mucinous adenocarcinomas, resulting in potentially incorrect results. Data on the accuracy and clinical relevance of this most recent consensus-based classification is largely lacking. Studies included in this thesis tried to answer these relevant research questions, and showed that in patients with appendiceal adenocarcinoma, mucinous histologic subtype was still of prognostic relevance, but only in patients with peritoneal dissemination (median overall survival 31.2 vs. 13.3 months, HR 0.42, 95%CI 0.28-0.62). Histologic subtype was no prognostic factor in patients with systemic metastases, defined as metastases outside the peritoneal cavity, or in patients with locoregional disease. Probably, the prognostic relevance of histologic subtype in peritoneal disease is a reflection of the differences in natural disease course, as mucinous and signet ring cell adenocarcinomas could cause PMP, whereas non-mucinous adenocarcinomas more frequently cause usual peritoneal metastases[49, 50]. As already stated in TNM-8, in which mucinous and non-mucinous appendiceal adenocarcinoma should be classified separately, it is of importance to subdivide these patients with an appendiceal adenocarcinoma, as it has prognostic implications[51].

Additionally, this thesis showed that each subtype of mucinous appendiceal neoplasm has a distinct clinical disease course in the metastatic setting. The 5-year survival rate of patients with low-grade PMP of a disseminated LAMN was more than twice as high as it was for patients with high-grade PMP of a mucinous adenocarcinoma. Also previous research showed evident differences in survival in patients with low-grade PMP, previously known as diffuse peritoneal adenomucinosis (DPAM) and high-grade PMP (peritoneal mucinous carcinomatosis; PMCA), in which higher survival rates were achieved in patients with low-grade PMP, even after correction for intensive treatment with CRS+HIPEC[52-55]. The obtained results show the need to subdivide patients with low- and high-grade PMP according to the latest proposed consensus-based histopathological classification. However, as all types of PMP are classified with one corresponding morphologic code (8480/6), research could be challenging[56]. Therefore, it could be suggested for the ICD-O-4 to separately classify PMP with either a differing morphologic code, or, a more realistic option, to better subdivide the tumour behaviour of the PMP into low-grade (8480/5) and high-grade (8480/6).

Methodological considerations

Netherlands Cancer Registry

The studies included in this thesis are based on data of the Netherlands Cancer Registry, in which data of all newly diagnosed malignancies in the Netherlands is collected. Although much information regarding patient and tumour characteristics, diagnosis and initial treatment are recorded, several important details are lacking due to its population-based nature, especially in rare tumours. For instance, in patients with metastatic SBA, extensive data on the type and duration of systemic treatment regimen are not routinely collected. Therefore, for chapter 3&4 in this thesis, additional data was retrospectively collected on systemic treatment regimen for patients treated with palliative systemic therapy for synchronous metastases of SBA diagnosed between 2007 and 2016 by registry clerks of the Netherlands Cancer Registry. Moreover, data on several prognostic factors are lacking, including clinical performance status, comorbidities, extent of the metastatic disease, disease related symptoms, the serum levels of tumour markers and the mutational status of the primary tumour such as RAS/BRAF/MSI. Also information regarding metachronous disease, second-line treatment, repeated treatment procedures and the reasons to (not) administer patients a specific therapy is missing, which is a potential pitfall.

Study design

All studies in this thesis had an observational design and were based on every day clinical data. Although randomised controlled trials (RCTs) are considered as the gold standard for determining the precise effect of new treatments, biomarkers or other prognostic and predictive factors, by minimising the risk of bias by confounding through randomisation, the external validity might be limited[57]. Population-based observational studies have a superior external validity, as it provides insights into the outcomes of unselected patients in daily clinical practice. Population-based research is especially highly valuable in the subset of patients who do not meet the eligibility criteria for RCTs or patients with rare diseases, in which RCTs are hard to conduct. In this thesis, insights were derived into both prognostic factors and the use and effects of treatments in patients with small bowel and appendiceal cancer, by combining the nationwide clinical data of patients with these rare diseases in consecutive years. Nevertheless, population-based research is prone to several biases, which should be considered when interpreting the results in this thesis.

Selection bias

Selection bias was present in many studies included in this thesis, particularly in the studies in which the role of therapy was addressed. For instance, baseline characteristics between the treated and non-treated differed (chapter 4), and even the patient characteristics between the different treatment strategies varied (chapter 3&4). One should take these

pretreatment differences into account, as in clinical practice the treating physician already decided how to treat a patient, in which the decision could be partly based on the patient's prognostic profile. Consequently, it could be hard to establish the true effect of a treatment in population-based research, as the differences in outcomes may not reflect the effect of the treatment, but rather the differences in patient- and tumour characteristics. For this reason, multivariable regression models were performed to determine the effect of a dependent prognostic factor, such as histologic subtype (chapter 7), adjusted for several patient and tumour characteristics. In order to eliminate potential endogeneity bias, propensity score matching was also used in chapter 5 to compare patients with and without additional bevacizumab beside palliative chemotherapy in metastatic SBA. In this study, propensity scores were determined by means of a logistic regression model in which the administration of bevacizumab in first-line treatment was the variable of interest, and the independent variables were those factors that were significant in univariable logistic regression, in combination with relevant clinical features. Patients were matched within tight bounds of the propensity scores, in which the predicted probability could not vary more than 1%. However, even after propensity score matching, it is still possible that patient groups are not totally comparable, due to the impossibility of gathering information on all prognostic factors.

Immortal time bias

Several studies in this thesis may have been exposed to immortal time bias, as patients should be alive to receive treatment. After initial diagnosis, a period of immortal time arises until a patient receives a type of treatment, either surgical or systemic. Especially in the studies on palliative systemic treatment (chapter 4&5), immortal time bias should be considered, in particular for the patients treated with second- or third-line treatment. Unfortunately, it was not possible for all included patients to determine the exact time of initial start of therapy. Otherwise, survival time could have been defined from the date of treatment, instead of date of diagnosis.

Stage migration

Stage migration should be considered when interpreting trends in treatment and (stage specific) survival. Improved diagnostic techniques, especially in the area of diseases with non-specific symptoms as small bowel and appendiceal cancer, could have led to an earlier detection of both the primary and metastatic disease. Small metastases, which were previously invisible on historic imaging techniques, could nowadays be visualized at an earlier stage than in a previous time period, causing the suggestion of an increase in metastatic rate (chapter 2&3). In chapter 2, it was shown that the proportion of patients presenting with metastatic disease of SBA increased over time, and, particularly, an increase

in patients diagnosed with multiple metastatic sites were seen, which can be attributed to stage migration.

Residual confounding

As the studies included in this thesis covered rare gastrointestinal cancers, by definition only relatively small numbers of patients are included. Consequently, it is possible that in several grouped patient and tumour characteristics over-aggregation occurred, as control of confounding might have not been tight enough. For example, in chapter 3 it was shown that elderly patients (≥70 years) had a lower chance to receive first-line combination chemotherapy and second-line treatment. Potentially, if the number of included patients was higher, it could be hypothetically possible that only elderly patients ≥75 or 80 years were at risk for receiving less first-line combination chemotherapy, and not those patients with an age of 70-75 years, which might have caused residual confounding. Moreover, as not all prognostic factors could be collected, due to the population-based nature of the Netherlands Cancer Registry, is it possible that additional confounders were not considered, also resulting in residual confounding.

Implications for clinical practice

As shown in this thesis, rare cancers, to which small bowel and appendiceal cancer belong, are associated with worse survival rates compared to more frequently encountered tumours, which is mainly caused by the combination of a diagnostic delay and the ignorance and unfamiliarity of physicians with potential treatment options, in partly due to the lack of clinical trials[58].

In patients with synchronous metastases of SBA, palliative chemotherapy without the addition of the targeted agent bevacizumab should be considered in daily practice. An oxaliplatin-based combination regimen of CAPOX or FOLFOX could be suggested as frontline regimen in metastatic SBA. The prescription of irinotecan-containing chemotherapy could be a reasonable option for second-line treatment. However, patient and tumour related prognostic factors should be taken into account to determine the best suitable treatment for each individual patient.

In patients with appendiceal cancer, histologic subtype is a highly important prognostic factor, which should be taken into consideration for potential treatment purposes. Especially in patients with isolated peritoneal dissemination of appendiceal adenocarcinomas, who are potential candidates for extensive treatment with CRS+HIPEC, histologic subtype should be considered. In the subgroup of patients with mucinous appendiceal neoplasms, it is of utmost importance to subdivide patients with low- and high-grade lesions according to the latest proposed consensus-based histopathological classification for both treatment and prognostic purposes.

Centralisation of pathologic diagnosis and treatment

In recent years, centralisation of care has significantly improved overall survival in patients with upper gastrointestinal cancers and rare cancers as head or neck cancer and sarcomas[59-63]. By centralising surgical treatment in oesophageal, gastric and pancreatic cancer, several improvements in patient related outcomes were seen, including an increase in resection rates, decline in postoperative mortality and a major increase in overall survival[61-65]. Also in patients treated with palliative systemic therapy in metastatic disease for oesophageal, gastric and pancreatic cancer, a higher survival was observed in patients treated in high-volume centers[66-68]. These improvements were caused by the enhanced experience of medical specialists and an improved infrastructure for patient management, which are various positive aspects of centralisation of care[63, 66].

Given the improvement of patient outcomes in other rare and upper gastrointestinal cancers by the centralisation of care, attempts should be made to centralise patient care

for small bowel and appendiceal cancer to obtain equivalent results in these patients. However, in patients with appendiceal cancer, centralisation of care should not only focus on oncologic treatment, but also on pathologic diagnosis. Previous research has shown that second review of pathologic tissue sections by a subspecialist pathologist improves patient outcome, by a spectacular decrease in diagnostic errors equal to 30-50%[69]. By centralising the pathologic assessment of rare appendiceal tumours, a decrease in misdiagnosis and misclassification is expected, leading to an enhanced patient management and potentially improved survival rates.

Notably, already a part of the surgical treatment procedures are centralised for patients with small bowel and appendiceal cancer. For instance, for patients with locoregional duodenal cancer in the upper part of the duodenum and PMP of appendiceal mucinous neoplasms, the surgical procedures pylorus preserving pancreaticoduodenectomy (PPPD) and CRS+HIPEC are concentrated in some high-volume centres nowadays[70]. As these high-volume centres for PPPDs and CRS+HIPEC already gained experience over the years with patients with small bowel and appendiceal cancer across the total treatment pathway, including all cooperating specialisms of pathologists, radiologists and medical oncologists in multidisciplinary teams, further centralisation of care for patients with small bowel and appendiceal cancers would be easy to establish. Hopefully, the further enhanced experience of medical specialists and the better infrastructure for patients with these rare diseases, leads to an improved identification of patients profiting from several treatment options and increased survival rates.

Implications for future research

As small bowel and appendiceal cancer are rare, it seems very hard to conduct large prospective observational or randomized trials in the future. Efforts should be made to improve patient care in patients with these rare diseases by international cooperation of specialised tertiary medical centres through exchange of their expertise and knowledge, and the creation of a large international prospective database, in which extensive patient baseline characteristics, tumour characteristics, and details on prognostic factors and treatment would be collected. Consequently, pretreatment differences between patients and the impact of prognostic factors could be better established, serving as an entry for improved patient management, for both curative and palliative treatment, as well as for best supportive care.

If centralisation of care for patients with small bowel and appendiceal cancer is realized, its effects on patient outcomes should be studied to determine its superiority to present clinical practice. Moreover, by concentrating care for patients with rare tumours, patients could more easily be enrolled in future clinical studies, which could be designed and performed for investigating several potential treatment options. For instance, as 91% of the patients with SBA has a potentially targetable genomic alteration, the role of other targeted agents should be further investigated by the development of n-of-1 clinical trials, also in order to personalize patient care[71].

Concluding remarks

In daily practice, patients with small bowel and appendiceal cancers have historically been treated in a similar fashion as frequently encountered gastrointestinal cancers, mainly as colorectal or gastric cancer. However, the rationale for this extrapolation is not evidence-based and therefore, this thesis aimed to provide insights into clinical and pathological aspects of these two rare gastrointestinal cancers. It was shown that small bowel and appendiceal cancer both have a distinct clinical disease course, compared to other gastrointestinal cancers. Metastatic disease was common in patients with SBA, and only a minority was treated with palliative systemic treatment. An oxaliplatin-containing regimen could be a suggested frontline regimen, without the addition of the targeted agent bevacizumab. In appendiceal cancer, histologic subtype is of prognostic relevance in mainly peritoneal disease, and it is of utmost importance to classify patients with mucinous appendiceal neoplasms according to the latest proposed consensus-based classification for prognostic and treatment purposes.

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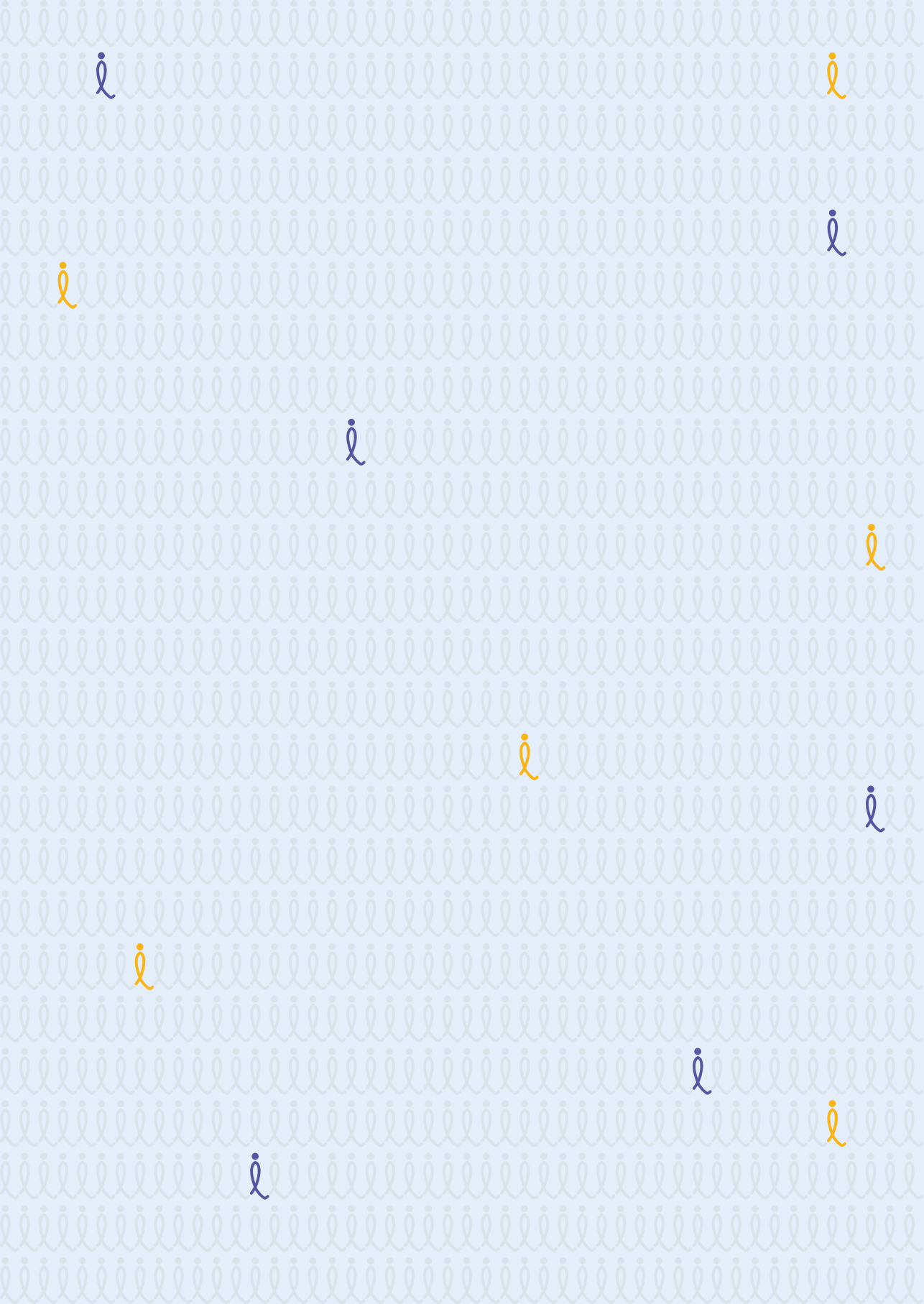


Nederlandse samenvatting

Dutch summary

Inleiding

Wereldwijd komt kanker in het maag-darmkanaal veelvuldig voor, waarvan dikkedarmkanker het meest voorkomend is. Andere veelvoorkomende vormen van kanker in het maag-darmkanaal zijn lever-, maag- en slokdarmkanker. In 2018 had wereldwijd 28% van de patiënten die gediagnosticeerd werd met kanker, een tumor in het maag-darmkanaal. Alleen al in Nederland werden in 2018 maar liefst 13.900 patiënten gediagnosticeerd met dikkedarmkanker.

Dunne darm- en appendixkanker zijn daarentegen zeldzame vormen van kanker in het maag-darmkanaal, waarmee jaarlijks slechts enkele honderden patiënten worden gediagnosticeerd. Zo werden in Nederland in 2018 slechts 300 patiënten gediagnosticeerd met dunnedarmkanker en 200 met appendixkanker. Door het zeldzame karakter van deze tumoren, is er weinig onderzoek verricht naar deze tumorsoorten. In de dagelijkse praktijk worden patiënten met dunne darm- en appendixkanker daarom vaak beschouwd en behandeld als maag- of dikkedarmkanker. Echter is het onduidelijk of dunne darm- en appendixkanker zich op eenzelfde manier gedragen als maag- en/of dikkedarmkanker, waardoor het onbekend is of de gangbare behandelingen voor maag- en dikkedarmkanker ook een soortgelijk positief effect hebben op de overleving van patiënten met dunne darm- en appendixkanker.

Daarbij zijn door het zeldzame karakter van dunne darm- en appendixkanker grote klinische studies vaak niet mogelijk of lastig uit te voeren, omdat er niet genoeg patiënten geïncludeerd kunnen worden. Hierdoor is het bestaande en uitgevoerde onderzoek vaak gebaseerd op patiënten en resultaten uit het verleden en veelal afkomstig van gespecialiseerde behandelcentra, waardoor dit geen goede afspiegeling is van de dagelijkse klinische praktijk.

Doel van dit proefschrift

Het doel van dit proefschrift is om inzicht te verkrijgen in de klinische en pathologische aspecten van dunne darm- en appendixkanker, door het bestuderen van de epidemiologie (de leer van het optreden en de verspreiding van ziekten in de bevolking en de kennis van factoren die hierop van invloed zijn), het ziektebeloop, de behandeling en prognostische factoren van deze twee zeldzame tumoren in het maag-darmkanaal. De belangrijkste doelstellingen van dit proefschrift zijn:

- Inzicht geven in de epidemiologie van locoregionale (niet uitgezaaide) en gemetastaseerde (uitgezaaide) dunnedarmkanker, door het bestuderen van de incidentie (het aantal nieuwe patiënten met een ziekte per jaar), behandeling en overleving van patiënten over de tijd (deel I).
- Evalueren van het gebruik en de effecten van palliatieve systemische therapie (behandeling met chemotherapie of doelgerichte therapie, die niet meer gericht is op genezing) bij patiënten met uitgezaaide dunnedarmkanker (deel II).
- Onderzoeken van de prognostische waarde van histologisch subtype (verschillende type weefsels) en de impact hiervan op de behandeling en overleving bij patiënten met appendixkanker (deel III).

Belangrijkste bevindingen

In deel I van dit proefschrift wordt inzicht gegeven in de epidemiologie van dunnedarmkanker. In **hoofdstuk 2** wordt de incidentie, behandeling en overleving van patiënten over tijd met locoregionale en gemetastaseerde dunnedarmkanker (subtype: adenocarcinoom) weergegeven. In deze studie werd gevonden dat de incidentie van dunnedarmkanker toenam over de tijd, wat voornamelijk kwam door een toename van het aantal patiënten met een tumor in de twaalfvingerige darm. Ook presenteerden zich meer patiënten met uitgezaaide ziekte in verloop van de tijd. Zo steeg dit percentage van 27% van de patiënten in de periode 1999-2003 tot bijna 40% in 2009-2013. In het geval van uitzaaiingen, hadden de meeste patiënten uitzaaiingen in de lever (46%) en het peritoneum (buikvlies, 29%), al was dit afhankelijk van de primaire locatie van de tumor. Patiënten met een tumor in de twaalfvingerige darm hadden vaker leveruitzaaiingen (54%), terwijl patiënten met een tumor verderop in de dunne darm vaker buikvliesuitzaaiingen (44%) hadden. Ondanks het toenemende gebruik van palliatieve chemotherapie, hadden patiënten met uitgezaaide ziekte een overleving van ongeveer 4-5 maanden.

In **hoofdstuk 3** worden de resultaten van de studie naar de incidentie, risicofactoren, behandeling en overleving van patiënten met buikvliesuitzaaiingen van dunnedarmkanker (subtype: adenocarcinoom) getoond. In 13% van alle patiënten met dunnedarmkanker was

er sprake van buikvliesuitzaaiingen. In vergelijking met alle patiënten met dunnedarmkanker, waren patiënten met buikvliesuitzaaiingen vaak jonger en hadden ze vaker een tumor verderop in de dunne darm (na de twaalfvingerige darm). De overleving van patiënten die geen tumorgerichte behandeling kregen, was slechts 2.5 maand. Patiënten die behandeld werden met palliatieve chemotherapie leefden ongeveer 11 maanden, tegenover 32 maanden in een strikt geselecteerde groep patiënten die CRS+HIPEC hadden ontvangen. CRS+HIPEC is een combinatie van een operatie waarbij alle zichtbare tumorresten worden verwijderd (cytoreductieve chirurgie; CRS), waarna de buik gespoeld wordt met verwarmde chemotherapie (HIPEC).

In **deel II** van dit proefschrift worden het gebruik en de effecten van palliatieve systemische therapie bij patiënten met gemetastaseerde dunnedarmkanker (type: adenocarcinoom) geëvalueerd, waarbij in **hoofdstuk 4** wordt ingegaan op palliatieve chemotherapie. In deze studie werd gevonden dat slechts 38% van de patiënten met uitgezaaide ziekte palliatieve chemotherapie had ontvangen in de periode 2007-2016. Patiënten die behandeld werden met palliatieve chemotherapie waren een stuk jonger dan onbehandelde patiënten (63 vs. 72 jaar). Als aanvangstherapie ontving 80% van de patiënten combinatiechemotherapie (meer dan 1 middel), voornamelijk CAPOX of FOLFOX. Patiënten die behandeld werden met monotherapie (1 middel) kregen in 86% van de gevallen capecitabine. Oudere patiënten (70+) werden vaker behandeld met monotherapie dan met combinatiechemotherapie. Tweedelijnsbehandeling (de opvolgende behandeling na aanvangstherapie) werd slechts voorgeschreven aan 27% van de behandelde patiënten, waarbij irinotecan het meest voorgeschreven middel was. De overleving van patiënten behandeld met chemotherapie bedroeg 9.3 maanden, vergeleken met 3.0 maanden bij patiënten die niet behandeld waren met palliatieve chemotherapie. Patiënten die alleen behandeld waren met aanvangstherapie, en geen opvolgende lijn behandeling hadden gekregen, hadden een overleving van 7.0 maanden na combinatiechemotherapie en 5.6 maanden na monotherapie.

In **hoofdstuk 5** wordt vervolgens het gebruik en effect van doelgerichte therapie, naast het gebruik van palliatieve chemotherapie, geëvalueerd bij patiënten met uitgezaaide dunnedarmkanker. Hierbij werd gevonden dat slechts 13% van de patiënten bij aanvang behandeld werd met aanvullende doelgerichte therapie, naast chemotherapie. Hierbij werd alleen het doelgerichte middel bevacizumab voorgeschreven. In 96% van de gevallen was dit in combinatie met combinatiechemotherapie met CAPOX of FOLFOX. Patiënten met een ileumtumor (laatste stuk dunne darm grenzend aan de dikke darm) kregen vaker bevacizumab voorgeschreven dan patiënten met dunnedarmkanker in een ander deel van de dunne darm. De overleving van patiënten die behandeld waren met chemotherapie zonder bevacizumab was 9.3 maanden, tegenover 9.1 maanden in de groep patiënten die

wel behandeld was met bevacizumab in combinatie met chemotherapie. Als wederom weer gekeken werd naar patiënten die alleen behandeld waren met aanvangstherapie, zonder opvolgende lijn behandeling, was de overleving 6.8 maanden voor patiënten na chemotherapie, vergeleken met 8.5 maanden bij patiënten die behandeld waren met chemotherapie en bevacizumab.

Deel III van dit proefschrift beschrijft de prognostische waarde van histologisch subtype bij patiënten met appendixkanker, waarbij vooral gekeken is naar mucineuze (slijmvormende) tumoren. De afgelopen jaren werden wereldwijd verschillende classificaties gehanteerd voor mucineuze appendixtumoren. Door voortschrijdende inzichten is in 2017 een op consensus gebaseerde internationale classificatie opgesteld door experts om zo eenduidig mucineuze appendixtumoren te kunnen classificeren. In **hoofdstuk 6** worden de verschillende histologische subtypes bij patiënten met mucineuze appendixtumoren uitgediept aan de hand van deze nieuwe classificatie. Mucineuze appendixtumoren kunnen onderverdeeld worden in 3 subgroepen, namelijk in 1. premaligne (voorstadia van kanker) laesies, ook wel adenomen genoemd, 2. tumoren die mogelijk kwaadaardig kunnen worden, onderverdeeld in laaggradige en hooggradige laesies, die bekend staan als LAMN (laaggradige mucineuze appendixtumoren) en HAMN (hooggradige mucineuze appendixtumoren) en 3. de maligne (kwaadaardige) laesies, waaronder de mucineuze adenocarcinomen en zegelringcel adenocarcinomen. Verder wordt ingegaan op pseudomyxoma peritonei (PMP), de term die gebruikt wordt voor naar het buikvlies uitgezaaide ziekte door mucineuze appendixtumoren. PMP onderscheidt zich van klassieke buikvliesuitzaaiingen door de aanwezigheid van grote hoeveelheden slijm in de buikholte. Net als bij mucineuze appendixtumoren, kan PMP ook onderverdeeld worden in verschillende categorieën, namelijk in 1. acellulair (geen cellen aanwezig in het slijm) PMP, 2. laaggradig PMP, 3. hooggradig PMP en 4. hooggradig PMP met zegelringcellen. Laaggradig PMP wordt in de meeste gevallen veroorzaakt door een primaire LAMN, hooggradig PMP door een mucineus adenocarcinoom en hooggradig PMP met zegelringcellen door een zegelringcel adenocarcinoom.

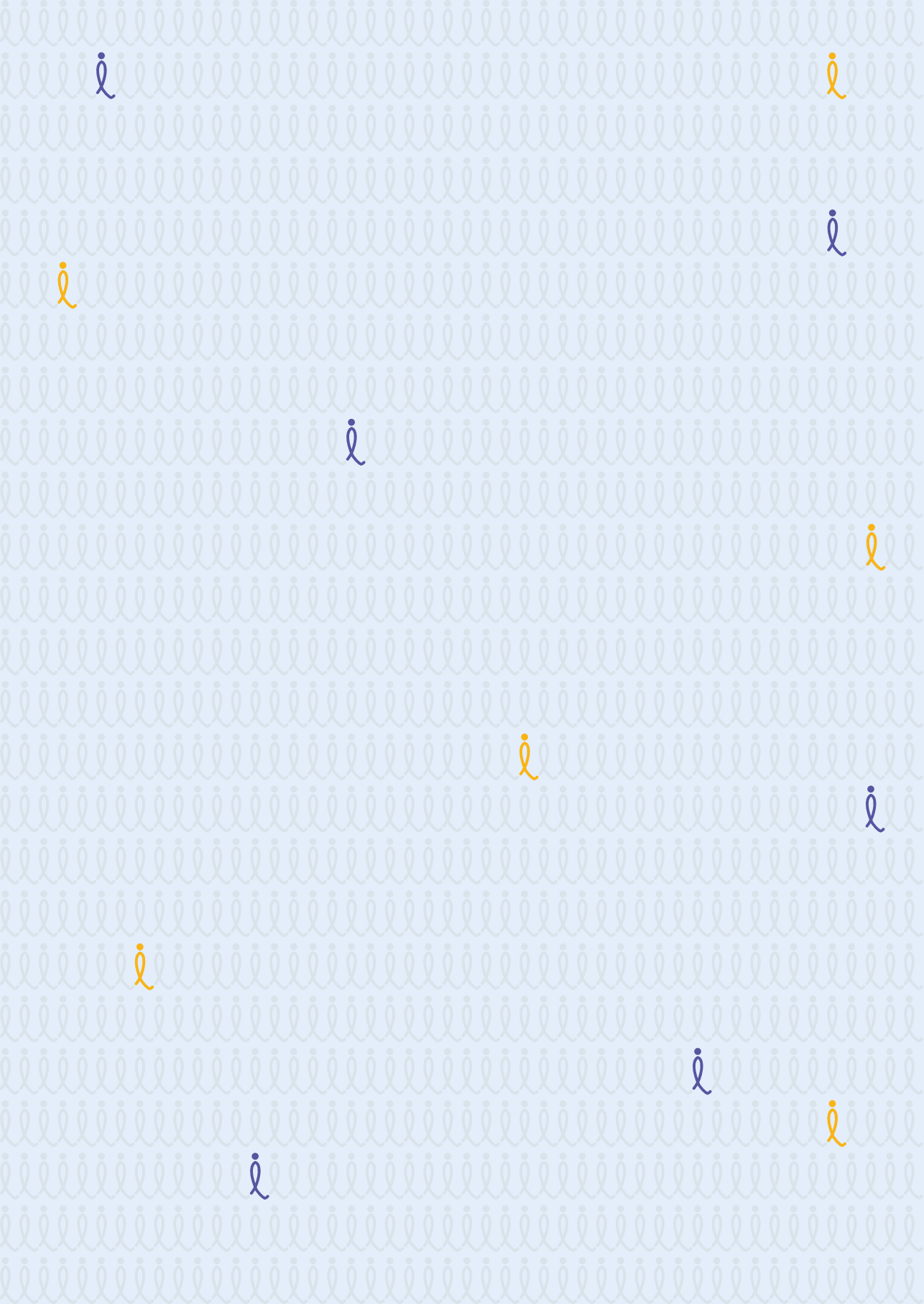
In **hoofdstuk 7 en 8** wordt verder ingegaan op mucineuze appendixtumoren, waarbij gebruik gemaakt is van aanvullende data van het Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA; de landelijke Nederlandse pathologiedatabase). In **hoofdstuk 7** wordt de prognostische waarde van histologisch subtype bij patiënten met appendixtumoren beschreven, waarbij gekeken is naar patiënten met mucineuze, niet-mucineuze (niet slijmvormende) en zegelringcel adenocarcinomen in de periode 2001 tot 2015. Hierbij werd gevonden dat bij niet uitgezaaide ziekte, histologisch subtype niet van prognostische waarde was op de overleving van patiënten. In het geval van uitgezaaide ziekte, hadden patiënten met mucineuze adenocarcinomen een betere overleving dan

patiënten met niet-mucineuze adenocarcinomen, namelijk 27.7 maanden tegenover 12.6 maanden. Echter, indien gekeken werd naar de locatie van uitzaaiingen, werd gezien dat patiënten met mucineuze tumoren alleen een betere overleving hadden in het geval van buikvliesuitzaaiingen, maar niet in het geval van uitzaaiingen elders in het lichaam.

Door de verschillende histopathologische classificaties voor mucineuze appendixtumoren in de afgelopen 20 jaar en de toenmalige onbekendheid van de subtypen LAMN en HAMN bij clinici en pathologen, is het mogelijk dat uit vroeger onderzoek conclusies zijn getrokken, die hedendaags niet meer kloppen met de voortschrijdende inzichten. Daarom werd in **hoofdstuk 8** het ziektebeloop van bepaalde typen uitgezaaide mucineuze appendixtumoren, namelijk LAMN, HAMN en mucineuze adenocarcinomen beschreven en geëvalueerd. In de periode 2001 tot 2015 waren er 235 patiënten in Nederland geregistreerd als hebbende een uitgezaaid mucineus adenocarcinoom of PMP. Na herbeoordeling van de pathologieverslagen en enkele pathologische preparaten van deze patiënten, bleek dat 136 (57.8%) patiënten een uitgezaaid LAMN hadden, 2 (0.9%) een uitgezaaid HAMN en 97 (41.3%) een uitgezaaid mucineus adenocarcinoom. Er werd gevonden dat de overleving van patiënten afhankelijk was van het histologisch subtype, gezien na 5 jaar 78.9% van de patiënten nog in leven was met een uitgezaaid LAMN, tegenover 33.2% van de patiënten met een uitgezaaid mucineus adenocarcinoom.

Concluderende opmerkingen

In de dagelijkse praktijk worden patiënten met zeldzame dunne darm- en appendixkanker vaak behandeld op eenzelfde manier als andere veelvoorkomende maag-darmtumoren, zoals maag- en dikkedarmkanker. De onderbouwing hiervoor ontbreekt echter grotendeels. Dit proefschrift verschaft inzicht in de klinische en pathologische aspecten van dunne darm- en appendixkanker, door het bestuderen van de epidemiologie, het ziektebeloop, de behandeling en prognostische factoren bij deze twee zeldzame tumoren in het maag-darmkanaal. Dit proefschrift laat zien dat dunne darm- en appendixkanker unieke kankersoorten zijn, met ieder een zeer verschillend ziektebeloop. Patiënten met dunnedarmkanker werden vaak al bij diagnose gediagnosticeerd met uitgezaaide kanker, en slechts een kleine minderheid werd hiervoor behandeld met palliatieve systemische therapie. Combinatie-chemotherapie met oxaliplatin (CAPOX/FOLFOX) zou op basis van de resultaten in dit proefschrift gesuggereerd kunnen worden als aanvangsbehandeling voor patiënten met uitgezaaide dunnedarmkanker, zonder de toevoeging van het doelgerichte middel bevacizumab. Bij patiënten met appendixkanker is histologisch subtype van prognostische waarde, voornamelijk in het geval van naar het buikvlies uitgezaaide ziekte. Derhalve is het van belang om de weefsels van patiënten met mucineuze appendixtumoren te classificeren aan de hand van de nieuwste op consensus gebaseerde richtlijn voor mucineuze appendixtumoren, voor zowel therapeutische als prognostische doeleinden.



List of publications

Published articles

Legué LM, Bernards N, Gerritse SL, van Oudheusden TR, de Hingh IHJT, Creemers GJ, Ten Tije AJ, Lemmens VEPP. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: A population-based study in The Netherlands. *Acta Oncol.* 2016;55:1183-1189.

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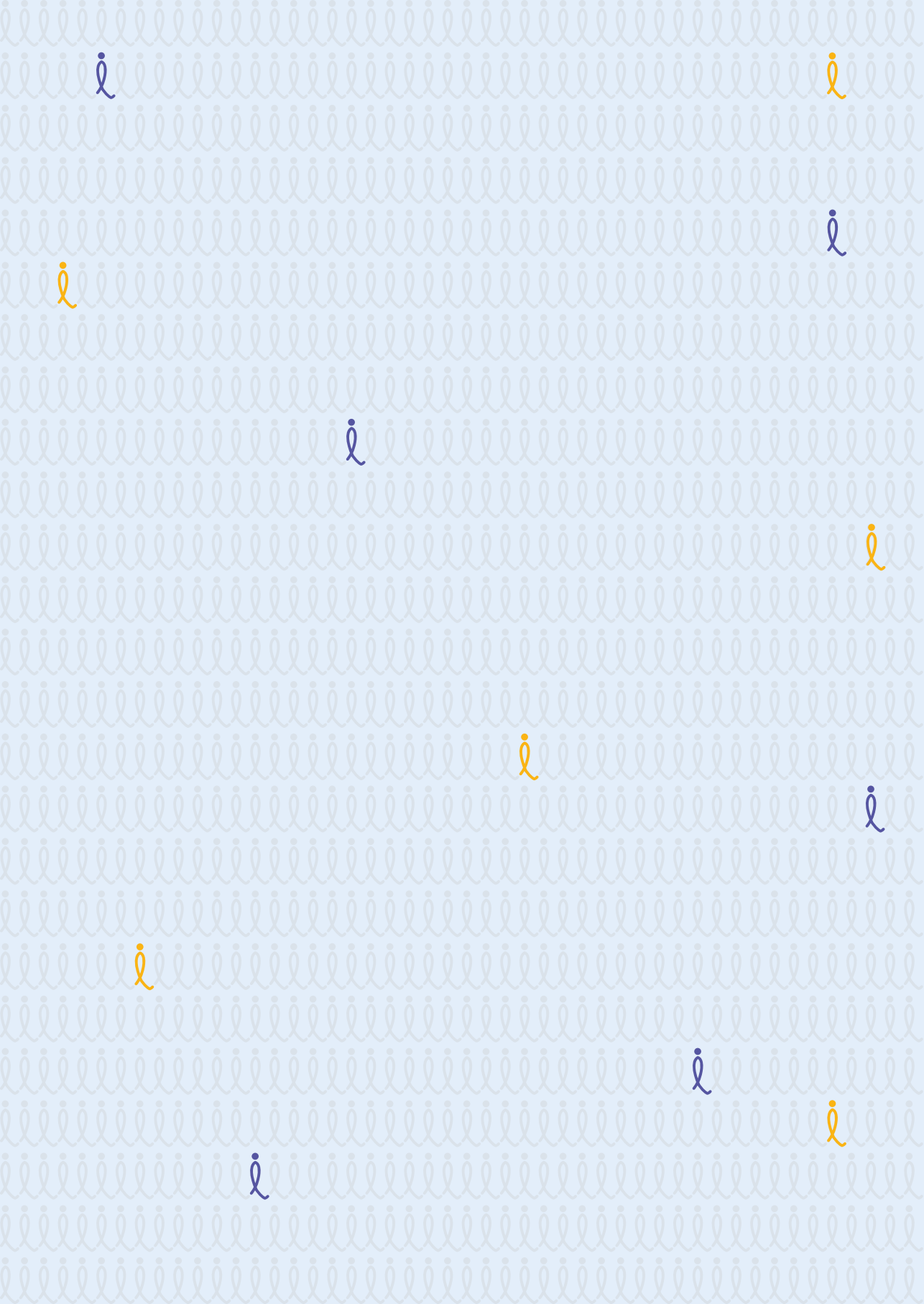
Legué LM, van Erning FN, Creemers GJ, Lemmens VEPP, de Hingh IHJT, Huysentruyt CJ. The prognostic relevance of histologic subtype in appendiceal adenocarcinoma. *Eur J Surg Oncol.* [Epub ahead of print].

Submitted

Legué LM, van Erning FN, Creemers GJ, Lemmens VEPP, de Hingh IHJT, Huysentruyt CJ. The clinical relevance of the histopathological classification for metastatic mucinous appendiceal neoplasms in a verified population-based cohort.



Dankwoord

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Dankwoord

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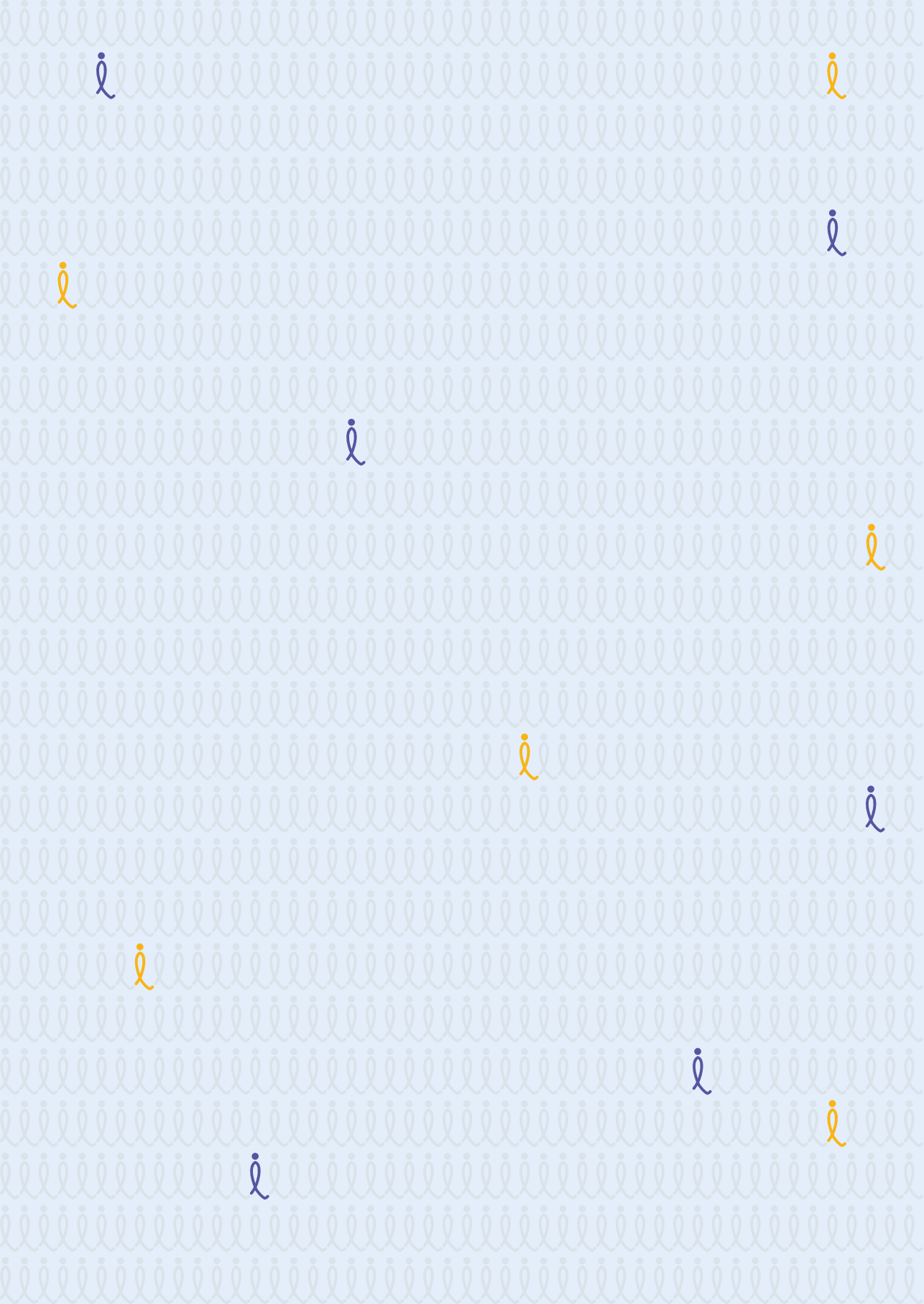
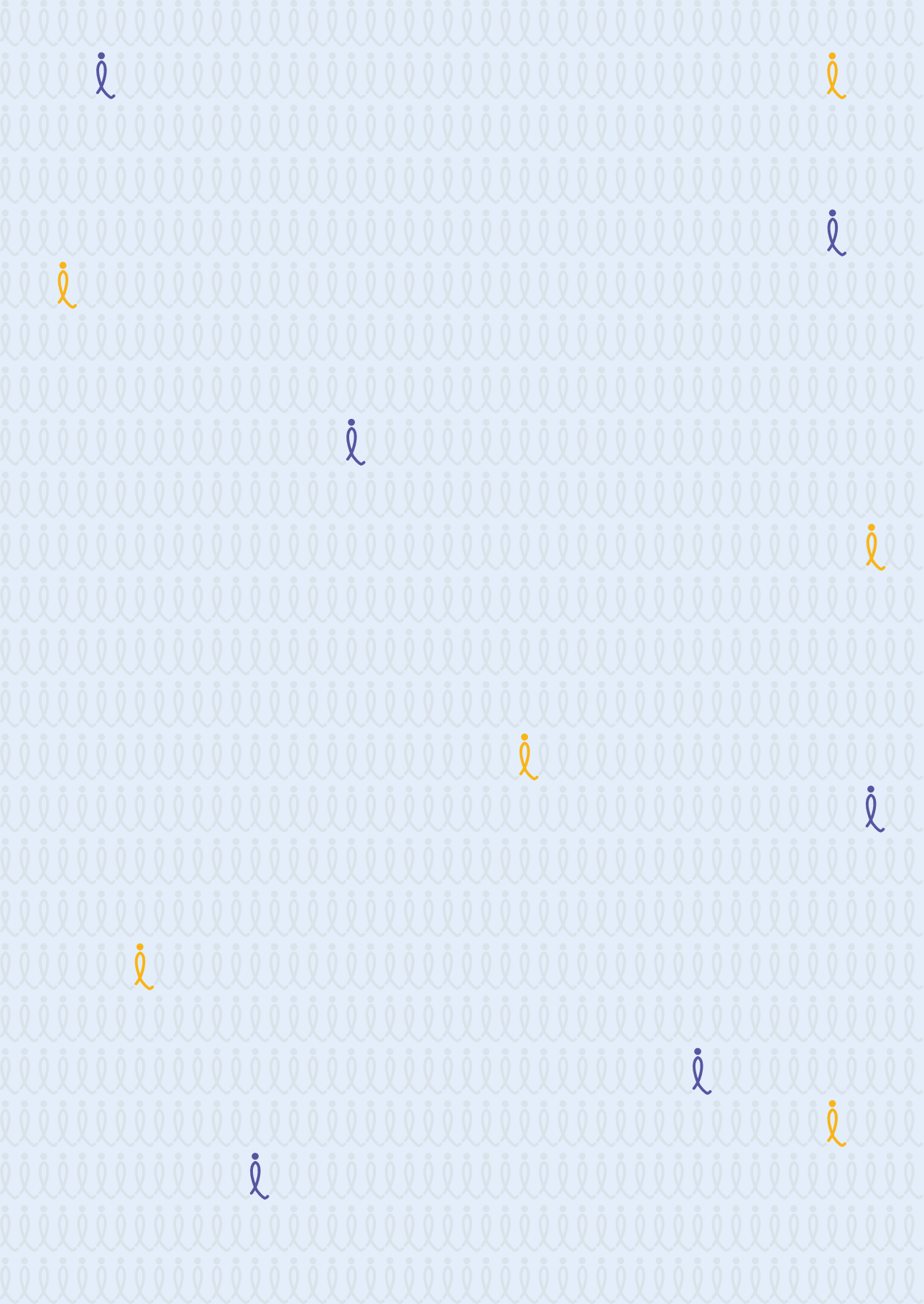


Curriculum vitae

Curriculum vitae

Laura M. Legué was born on the 20th of October 1993 in Houten, the Netherlands. She finished secondary education at the Utrechts Stedelijk Gymnasium in 2011. Subsequently, she started medical school at Maastricht University. In 2014 she received her Bachelor's degree in Medicine cum laude. After her first regular internship, she conducted her scientific internship with data of the Netherlands Cancer Registry. This internship focused on the incidence, treatment and survival of small bowel adenocarcinoma, under supervision of dr. G.J. Creemers and prof.dr. V.E.P.P. Lemmens. During her following regular internships, she continued doing research. In 2017, after receiving her Master's degree in Medicine cum laude, she started her PhD project at the Netherlands Comprehensive Cancer Organisation, on providing insight into the clinical and pathological aspects of small bowel and appendiceal cancer. At the same time, she started working as a resident not in training (ANIOS) in internal medicine, at the department of medical oncology of the Catharina Hospital for 3 days a week, under supervision of dr. G.J. Creemers. After completing her PhD, she started in September 2019 as a resident not in training (ANIOS) in internal medicine in the St. Antonius Hospital in Nieuwegein (head: dr. P.Chr. de Jong).



PhD Portfolio

PhD portfolio

Name PhD student:	Laura M. Legué
Erasmus MC Department:	Public Health/Netherlands Comprehensive Cancer Organisation (IKNL)
PhD period:	September 2017 – July 2019
Promotor:	Prof.dr. V.E.P.P. Lemmens
Copromotors:	Dr. G.J. Creemers
	Dr. F.N. van Erning

	Year	Workload Hours/ ECTS
Courses		
Wetenschappelijke Integriteit, Erasmus MC	2018	8
Masterclass presenteren, Catharina ziekenhuis	2019	8
Seminars and workshops		
10e Gastrointestinale symposium, IKNL	2016	4
Wetenschapsavond, Catharina ziekenhuis	2017	4
Pijn Spreekuur 2018, Bureau Prevents	2018	4
Regionaal Upper GI MDO Symposium, Catharina ziekenhuis	2018	4
Wetenschapsavond, Catharina ziekenhuis	2018	4
Wetenschapsavond, Catharina ziekenhuis	2019	4
Presentations		
Oral presentation, 10e Gastrointestinale symposium	2016	32
Poster presentation, 10th International Congress on Peritoneal Surface Malignancies (PSOGI)	2016	32
Oral presentation, 10th International Congress on Peritoneal Surface Malignancies (PSOGI)	2016	32
Oral presentation, Oncologieweek 2018	2018	32
Oral presentation, Nascholing oncologie voor fysiotherapeuten	2019	32
Oral presentation, Wetenschapsavond 2019	2019	32
Poster presentation, European Multidisciplinary Colorectal Cancer Congress (EMCCC)	2019	32

Conferences		
10th International Congress on Peritoneal Surface Malignancies (PSOGI)	2016	24
European Multidisciplinary Colorectal Cancer Congress (EMCCC)	2019	24
Supervising master's thesis		
Fatima Jid, 'An overview and outcomes of systemic therapy in patients with colorectal cancer in the Catharina Hospital'	2018-2019	80
Other		
Actualisatie Dunnedarmkanker, kanker.nl	2018-2019	64
Actualisatie Pseudomyxoma peritonei, kanker.nl	2019	64
ANIOS medische oncologie, Catharina ziekenhuis	2017-2019	2200
Total		2720